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BASE-CATALYSED CONDENSATION OF ARYL ALDEHYDES AND VALINE-DERIVED BOROXAZOLIDONES

Master of Science Thesis

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ABSTRACT

RAUNIO, JENNA: Base-catalysed condensation of aryl aldehydes and valine-derived boroxazolidones

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Keywords: imine condensation, organoboron compounds, N-B bond, boroxazolidones, aryl aldehydes, base catalysis

Imines are an important group of compounds for many chemical reactions in organic chemistry, mostly as electrophiles. In nature, imines are important for the transamination reaction. N-B bonds are interesting because they can be thought of as an analogy to a C-C bond. However, unlike a C-C bond, the N-B bond is polarized. Imines and N-B bond-containing compounds both have similar potentials as pharmaceuticals. Both of these groups can have antibacterial, antifungal and anticancer effects. The N-B bond focused on in this thesis is formed when an amino acid reacts with a boron compound to form a hetero ring structure known as a boroxazolidone.

In this master's thesis, the imine condensation between aldehydes and boroxazolidones, and the N-B bond were studied. Boroxazolidones with differing substituents at the boron were prepared from the corresponding triethylammonium tetra-arylborates (TEATABs) and (L)-valine. These were then reacted with different aryl aldehydes in the presence of a base as a catalyst to afford the corresponding imines. The general procedures for preparing the TEATABs, the boroxazolidones and imines had already been established in prior projects in the laboratory.

Two Lewis bases, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and sodium methoxide (NaOMe), were found to produce the most simple ketimine and aldimine respectively in good yields and without side products. However, the aldimine is very labile and reverts easily to its starting materials. When testing other aldehydes with TBD, it was found that the yields range from 63 to 0 %, in this general order depending on the aldehyde's substituents: halogen-substituted > electron withdrawing but non-halogen-substituted > electron donating. 4-Methoxybenzaldehyde was an exception to this because it produced a decent yield. Five different boroxazolidones were prepared from the corresponding TEATABs. The effect of the boroxazolidones' substituents at boron had a lesser effect on the imine yield than the aldehydes' substituents. Difluoro- and methyl-substituted boroxazolidones produced good yields but the 4-methoxy-substituted boroxazolidone produced a much lower yield.

TIIVISTELMÄ

RAUNIO, JENNA: Emäskatalysoitu aryylialdehydien ja valiinista johdettujen boroksatsolidonien kondensaatio

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Avainsanat: imiinikondensaatio, organobooriyhdisteet, N-B-sidos, boroksatsolidonit, aryylialdehydit, emäskatalyysi

Imiinit ovat tärkeitä orgaanisessa kemiassa – lähinnä elektrofiileina. Luonnossa imiinit ovat tärkeitä transaminaatio-reaktion kannalta. Typpi-boori-sidokset ovat kiinnostavia, sillä ne ovat analogisia hiili-hiili-sidosten kanssa. Mutta toisin kuin hiili-hiili-sidokset, typpi-boori-sidokset ovat polarisoituneita. Sekä imiineillä että typpi-boori-sidoksen sisältävillä yhdisteillä on ominaisuuksia, jotka ovat kiinnostavia lääketieteessä. Niillä voi olla bakteereita, sieniä tai syöpää torjuvia vaikutuksia. Tässä opinnäytetyössä keskitytään typpi-boori-sidokseen, joka syntyy aminohapon reagoidessa booriyhdisteen kanssa muodostaen boroksatsolidonina tunnetun heterorenkaan.

Tässä diplomityössä tutkittiin aldehydien ja boroksatsolidonien välistä imiinikondensaatiota sekä typpi-boori-sidosta. Boroksatsolidoneja, joissa boori oli vaihtelevasti substituoitu, valmistettiin niitä vastaavista trieyyliammonium tetra-aryyliboraateista (TEATAB:eista) ja L-valiinista. Näistä boroksatsolidoneista ja erinäisistä aryylialdehydeistä valmistettiin vastaavia imiinejä. Imiinien muodostukseen vaaditaan katalyytiksi emäs. Trietyyliammonium tetra-aryyliboraattien, boroksatsolidonien ja imiinien valmistukseen tarvittavat reaktiot oli kehitetty jo aiemmissa projekteissa.

Kaksi eri Lewis-emästä – 1,5,7-triatsabisyklo[4.4.0]dek-5-eeni (TBD) ja natriumetoksidi (NaOMe) – tuottivat yksinkertaisimman ketimiinin ja aldimiinin hyvällä saannolla ilman sivutuotteita. Aldimiini on kuitenkin hyvin epävakaa ja palautuu helposti lähtöaineikseen. Useiden aldehydien testaus TBD:n katalysoimana tuotti saantoja 63 ja 0 %:n väliltä. Saanto riippui aldehydien substituenteista seuraavasti: halogeeni-substituoidut > elektroneja puoleensa vetävät ryhmät, jotka eivät sisällä halogeeneja > elektroneja työntävät ryhmät. 4-Metoksibentsaldehydi oli poikkeus tähän sääntöön, sillä sen reaktio tuotti tyydyttävän saannon. Viisi erilaista boroksatsolidonia valmistettiin vastaavista TEATAB:eista. Boroksatsolidonien boorin substituenttien vaikutus imiinin muodostumiseen oli pienempi kuin aldehydien substituenttien vaikutus. Difluori- ja metyyli-substituoidut boroksatsolidonit tuottivat suunnilleen yhtä hyvän saannon, mutta 4-metoksi-substituoitu boroksatsolidoni tuotti selvästi alhaisemman saannon.

PREFACE

This master's thesis was done for the Tampere University of Technology between January and October of the year 2016. I want to thank Professor Robert Franzén for introducing me to this topic and giving me the possibility of making a thesis about an interesting subject. I am especially grateful for Academy Research Fellow Nuno R. Candeias for all the help and support that he has given me over the course of doing this work. His advice and patience has been invaluable for this process. I also want to thank everyone else who worked in the laboratory and in the office for the positive and helpful atmosphere.

Finally, I want to thank my family, my partner and my friends for their support during this time.

Tampere 23.10.2016

Jenna Raunio

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ABBREVIATIONS AND NOTATIONS

^{13}C	carbon-13
^{1}H	proton
BNCT	boron neutron capture therapy
br. s.	broad singlet (NMR)
brine	saturated aqueous sodium chloride solution
CIAT	crystallization-induced asymmetric transformation
δ	chemical shift, ppm, (NMR)
d	doublet (NMR)
dd	doublet of doublets (NMR)
dquar	doublet of quartets (NMR)
dt	doublet of triplets (NMR)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DMSO	dimethyl sulfoxide
EDG	electron donating group
eq	molar equivalent
ether	diethyl ether
EWG	electron withdrawing group
EtOAc	ethyl acetate
i-PrMgCl	isopropylmagnesium chloride
J	coupling constant (NMR)
LB	Lewis base
m	multiplet (NMR)
MeOH	methanol
NaOMe	sodium methoxide
NaTAB	sodium tetra-arylborate
NMR	nuclear magnetic resonance
NOAEL	no-observed-adverse-effect level
Proton sponge	1,8-bis(dimethylamino)naphthalene
quar	quartet (NMR)
quin	quintet (NMR)
s	singlet (NMR)
solvent name-d_x	deuterated solvent
t	triplet (NMR)
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
t-BuOK	potassium *tert*-butoxide
TEATAB	triethylammonium tetra-arylborate
THF	tetrahydrofuran
TLC	thin-layer chromatography
wt%	weight percent

1. BACKGROUND

This thesis' foundation is in the doctoral thesis of Noora Kuuloja [1] and the master's thesis of Jenna Mannoja [2]. Kuuloja developed a method to produce N-B bond-containing ring structures called boroxazolidones from triethylammonium tetra-arylborates and (L)-valine [3]. Later studies found that these boroxazolidones could react with benzaldehyde to give two isomeric forms of imines, a ketimine and an aldimine.

Mannoja studied this imine formation reaction and found that by using different bases as catalysts, it was possible to form either the ketimine, aldimine or a mixture of them. Mannoja improved the reaction by finding the right equivalents of reagents, a good solvent and the right temperature. She found that unlike typically in imine condensation reactions, a Lewis acid does not work with this reaction and that water removal is not necessary [2].

The aim of this thesis is to further study this imine formation reaction and the N-B bond of boroxazolidones. This is done by first testing other bases in an attempt to further improve the reaction between benzaldehyde and the simplest boroxazolidone, which has two unsubstituted phenyl groups at the boron. This screening could give more information about what controls the formation of either the ketimine or the aldimine. After this, different aryl aldehydes are tested with the simplest boroxazolidone, and finally, different boroxazolidones are tested with benzaldehyde.

Chapter 2 gives background information about boron compounds, N-B bonds, boroxazolidones, tetra-arylborates and imines. Chapter 3 contains the results and discussion from the aforementioned reactions. Chapter 4 describes the procedures used in detail.

2. INTRODUCTION

2.1 General boron information

Boron is the fifth element and belongs to group 13 or IIIA in the periodic table. It is a metalloid and has a very high melting point of ~3400 K [4]. Boron has the electron configuration of $1s^2 2s^2 2p^1$. It is thought to be electron deficient because it has only three valence electrons and cannot easily form an octet by bonding. Boron has two stable isotopes, ^{10}B and ^{11}B with a ratio of about 1:4 in nature. Unlike aluminum, which belongs to the same group, boron does not form a trivalent cation. Because of its small size and high ionic potential, boron forms only covalent bonds, unlike aluminum. In nature, boron exists as mostly bound to oxygen as borates or boric acid and, much more rarely, to fluorine as BF_4^- [4]. Boron typically has a coordination number of three or four [5]. Coordination numbers of five and six are observed only in laboratory conditions [4]. Boron can adopt trigonal and tetrahedral geometries, which makes it an important element and boron chemistry a large field [6]. Boron is one of the vital inorganic elements needed by living organisms. Other such inorganic elements are, for example, phosphorus, manganese, molybdenum, copper and zinc. [7]

Boron is important for many purposes such as in glassware, fiberglass, laundry bleaches, fire retardants, fertilizers, metallurgy fluxes, insecticides, herbicides and reagents for chemical synthesis. The economically useful boron mineral deposits are rare, and in these, the boron is bound to oxygen. Boron is an essential micronutrient for plants but the exact mechanisms of boron in plants are unknown (year 1994). In higher amounts, it can be used to preserve wood and to control weeds or insects. [6] Boron can also be used for nuclear shielding [5] and in *boron neutron capture therapy* (BNCT) due to ^{10}B's large *neutron capture radius*. This makes boron compounds generally interesting for cancer treatments. [8]

Table 1: *End use of boron in the U.S in the year 2000 [5]*

Usage	%
Glass products	75.7
Sold to distributor / end use unknown	8.6
Soaps and detergents	6.5
Agriculture	3.9
Fire retardants	3.6
Miscellaneous	1.5
Metallurgy	0.1
Nuclear applications	0.1

For plants, boron plays a role in their metabolism, sugar translocation, pollen germination, hormone action, growth, nucleic acid synthesis and membrane function. Boron deficient plants suffer reduction of growth and finally death. Toxic amounts of boron result in leaf loss and loss of photosynthetic capacity. Plants usually tolerate between 0.3 to 4 mg of boron per liter in irrigation waters. In animals, boron has an effect on the maturation of growth plates in long bones (in chicks) and on the adsorption of calcium, magnesium and phosphorus (in mice). The *no-observed-adverse-effect level* (NOAEL) of boron in rats has been determined to be 9.6 mg/kg body weight/day. [5]

Any specific biochemical function for boron has not been found in humans. Regardless of this, it is still known that boron is needed, and it affects such things as metabolism, utilization of calcium, brain function, psychomotor response and the response to estrogen ingestion in menopausal women. The U.S. Environmental Protection Agency estimates the safe limit of boron in drinking water to be 0.6 mg of boron per liter. Raisins and peanuts contain a high amount of boron: over 1 mg of boron per 100 grams of food. Based on the previous NOAEL value, it has been calculated that a 60 kg person can acceptably consume 18 mg of boron per day. An average person consumes about 1 mg of boron per day. [5]

Precipitation, inorganic and organic sorption, ion exchange, membrane filtration and phytoremediation (use of plants to absorb boron) can be used to remove boron from water but none of these methods is cheap and effective at the same time. This is an important area if one wants to use seawater for drinking and irrigation as fresh water becomes scarcer. [5] Seawaters' boron comes mainly from rivers due to continental weathering and less so from the hydrothermal activities in the bottom of the seas. Boron is removed from the seas by inorganic processes such as adsorption to clay minerals. [7] When removing boron from water by membrane filtration, the pH-value is important because the charged species (scheme 1) can be better rejected by the membrane [9].

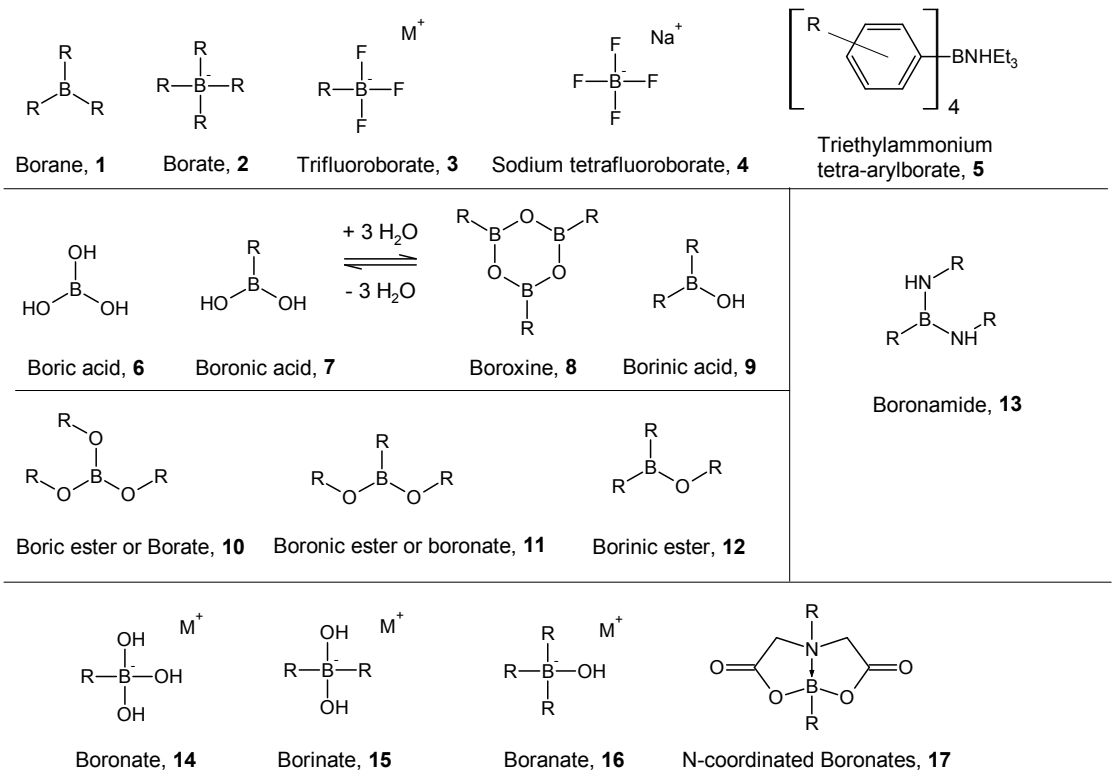
Boric acid $B(OH)_3$ is one of the forms of boron found in nature and the most common form of boron in water [5]. Depending on the source, boric acid is presented as a monobasic Lewis acid (LA) (eq 1) [4; 5] or as a tribasic Brønsted acid (eq 2 – 4) [9].

$H_3BO_3 + H_2O \rightleftharpoons H^+ + H_4BO_4^-$	pK_a 9.10 - 9.24	(eq 1)
$H_3BO_3 \rightleftharpoons H^+ + H_2BO_3^-$	pK_a 9.14	(eq 2)
$H_2BO_3^- \rightleftharpoons H^+ + HBO_3^{2-}$	pK_a 12.74	(eq 3)
$HBO_3^{2-} \rightleftharpoons H^+ + BO_3^{3-}$	pK_a 13.8	(eq 4)

Scheme 1: *Reactions of boric acid in water*

Boron nomenclature can be confusing. Picture 1 contains some boron compounds with their names. These names can change depending on the source, and a complete IUPAC system has not been developed yet [10]. Even picture 1 is inconsistent regarding the terms *boronate* and *borate* because two sources had assigned these names to different

compounds [10; 11]. The compounds are grouped based on whether the compounds have only B-R bonds, are acids, are esters, have tetravalent borons with B-O bonds or do not belong to these categories but are still mentioned (boronamide).



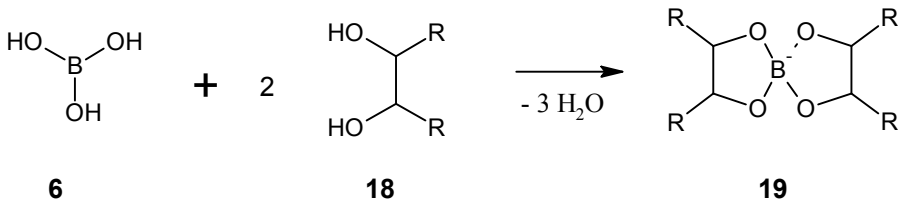
Picture 1: *Some boron compounds [10], [11], [12]*

Boric acid reacts with alcohols to give esters (Scheme 2). Typically, the equilibrium is on the left in aqueous solutions. In some cases, the equilibrium can be moved towards the products by removing water by, for example, adding an azeotrope-forming compound like toluene and removing the azeotrope by distillation [4].

$$\mathrm{B(OH)_3 + 3ROH \rightleftharpoons B(OR)_3 + 3H_2O}$$

Scheme 2: *Reaction of boric acid with an alcohol*

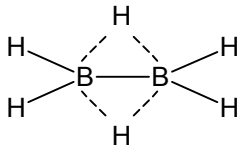
Some sugars can form ester-complexes with boric acid by reacting with its hydroxyl groups. Some antibiotics contain a tetrahedral boron atom in the middle of their structures. [6] Boric acid can react with *cis*-diols to form *boro-spiranes* [13].



Scheme 3: *Formation of boro-spirane **19** from boric acid **6** and a cis-diol **18***

Boro-spirane-formation and -dissociation might be important for the conversion of sugars to starch and cellulose in plants. [13] The stability of this complex is dependent on how well the orientation of the diol's hydroxyl groups matches with the tetrahedral coordination of the boron. Polysaccharide/borate complexes have been isolated from radish roots. In this case, the boron seems to be a part of the cell wall structure rather than a part of the metabolism of the plant. Borate/diol complexes might work as crosslinkers between polysaccharide chains in radish root tissue. In peas, B-deficiency causes cell walls to become thinner and finally results in cell breakage. However, it is not certain that cell wall structures are the reason for the essentiality of boron in plants. [4]

The borane BH_3 is not stable on its own, but it forms a *diborane* B_2H_6 structure with itself to become more stable. [13] This is a major difference when compared to the analogous carbon compound, methane.



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Picture 2: *Structure of diborane* ***20*** *[13]*

The boron in diborane still has a tetrahedral geometry but it can be thought to be pentavalent. These bonds involved in the pentavalent complex are called *three-center, two-electron bonds* [4]. Diborane can decompose and form more complex borane structures with the trend being that the more stable compounds have increasing boron to hydrogen atom ratios. The geometrical configuration of the more stable B_xH_y *polyboranes* or boron dihydrides resemble that of a sphere, where the borons are on the sphere's surface and the hydrogens are aligned outward. These boron hydrides can be thought to still be electron deficient, and they can react with electron donating substances like sodium and ammonia. This can form a complex, such as trimethylamine borane $[(CH_3)_3NBH_3]$, which enables the boron to have an electron-octet without the three-center bonding seen in diborane. Generally, the stronger the base, the more stable the resulting complex will be. The more stable polyboranes require stronger bases to form these complexes. [13] Ammonia borane (NH_3BH_3) and similar compounds (NH_xBH_x, x=4, 3, 2 or 1) are being investigated as possible hydrogen storage molecules. These kinds of compounds have much higher boiling points than the corresponding hydrocarbons and are solids at room temperature. [14]

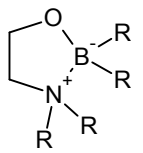
2.2 The N-B bond

The nitrogen-boron bond is an important research area because such compounds can have insecticidal, antineoplastic (prevents, inhibits or halts the development of a tumor), herbicidal, fungicidal and antibacterial effects. N-B bond -containing chemicals can also

work as surfactants where the N-B bond part works as the hydrophilic end [15]. An N-B bond can be thought of as an analogy for a C-C bond because they both have a tetrahedral character. The N-B bond's polarity causes the molecules to have higher melting and boiling points than the analogous compounds with a C-C bond. [13]

The basis for the bond's formation is nitrogen's ability to donate its electron pair to the electron deficient boron [16]. This covalent bond is sometimes called a *dative bond* or a *coordinative bond,* and it can be marked with an arrow (N→B) to show that the nitrogen is donating the electrons to the boron. IUPAC defines dative bond as an obsolete term because "The origin of the bonding electrons has by itself no bearing on the character of the bond formed" [17]. However, on another page they write, "In spite of the analogy of dative bonds with covalent bonds, in that both types imply sharing a common electron pair between two vicinal atoms, the former are distinguished by their significant polarity, lesser strength, and greater length." [18] Some sources make a differentiation between a dative N→B bond (ammonia borane, 130 kJ/mol bond energy) and a covalent N-B bond (solid boron nitride, 367 kJ/mol bond energy) [8]. The term dative bond or the arrow will not be further used in this thesis.

The following four paragraphs are based on papers studying 2-aminoethylborinates **21**. Unlike the 1,3λ^4,2λ^4,-oxazaborolidin-5-ones studied in this thesis and discussed in the next subchapter, compound **21** does not have a carbonyl in its ring.



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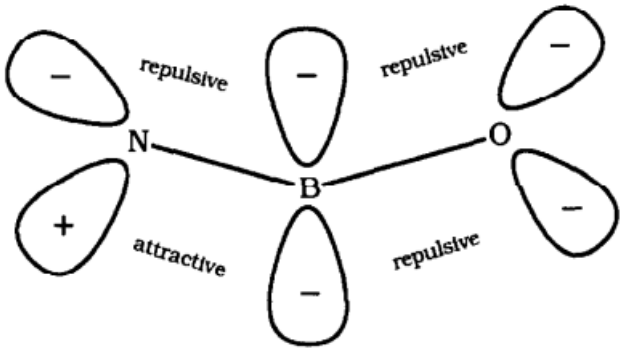
Picture 3: *Structure of 2-aminoethylborinate* ***21*** *[8]*

The N-B bond of a molecule is usually the primary target of nucleophilic reagents like water and other polar solvents, which can break the bond via hydrolysis [8]. The strength of the N-B bond depends on the Lewis basicity of the nitrogen and Lewis acidity of the boron. By adding electron donating groups (EDG) to the nitrogen and electron withdrawing groups (EWG) to the boron, the strength of the N-B bond should increase. Steric effects of the substituents also have to be taken into account. [19] In a five-membered ring containing an N-B-O system, the substituents of the two carbons also have an effect on the N-B bond. If the carbons' substituents have a steric hindrance against each other, the N-B bond will weaken. [20]

The following three paragraphs are based on purely theoretical ab initio calculations about the N-B-O system of 2-aminoethylborinates with the HF/6-31G** model. Six model molecules were studied with differing amounts of hydrogens or methyl groups at the boron and nitrogen. The electronegativities of boron, nitrogen, hydrogen and methyl are 3.88, 7.62, 7.18 and 7.45, respectively. Hydrogen has a higher electronegativity than

boron but lower than nitrogen. This causes the hydrogen to be positively charged when bound to nitrogen and negatively charged when bound to boron. This would explain why compounds like ammonia borane (NH_3BH_3) have a much higher boiling point than the corresponding hydrocarbon, ethane, because the hydrogen(s) at the boron and nitrogen can form hydrogen bonds between molecules [14]. Methyl is more electronegative than either the boron or nitrogen, so it is always negatively charged at both N and B. These *charge clouds* of different substituents can weaken or strengthen the N-B bond as seen in picture 4. [8]

Another term closely related to electronegativity is *electrostatic charge*, which is lower for nitrogen than for boron. Replacing the hydrogen with methyl will increase the electrostatic charge of nitrogen because the methyl is more electronegative than hydrogen. This also reduces the electrostatic charge difference between boron and nitrogen. If hydrogen is replaced with methyl at the boron, the boron's electrostatic charge also increases. However, boron has a higher electrostatic charge than nitrogen regardless of the N having a hydrogen or methyl substituent, so this causes the electrostatic charge difference between B and N to increase. This electrostatic charge difference is called *polarization across the bond*. This effect is not the same as Lewis acidity or basicity because it does not consider the *mesomeric effect*. The authors found an inverse relationship between the polarization across the N-B bond and the bond length and thus bond strength. This is in agreement with the previously made statements about making the nitrogen more Lewis basic by adding an electron-donating group like methyl and thus causing the N-B bond to be stronger. The authors suggest that some more electronegative groups than methyl could be used to further reduce the bond polarization and strengthen the N-B bond but the substituent cannot be too electronegative as not to reduce the Lewis basicity of the nitrogen too much. However, such calculations were not reported. [8]

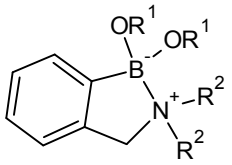


Picture 4: *An illustration of the substituents' electrostatic cloud interactions in an N-B-O system [8]*

In an N-B-O system, the substituents of the boron can also interact with the lone pairs of the oxygen. This can change the N-B-O system's geometry. A hydride on the boron has a stronger repulsive effect on the oxygen's lone pair than a methyl group, possibly

because the negative charge is more distributed in the methyl. [8] Other sources explain the N-B bond only via the Lewis acidity, Lewis basicity and steric effects of the substituents. No other source mentions polarization across the N-B bond or electrostatic charge differences between the substituents and the boron and nitrogen. In this thesis' context, the attractive effect caused by the positive charge cloud of the hydrogens bound to the nitrogen could mean that the boroxazolidones discussed in the next chapter are partially stabilized by this effect.

For an *o*-(*N*,*N*-dialkyl aminomethyl)arylboronate **22**, it was found that an aprotic solvent is necessary for the formation of the N-B bond. A protic solvent on the other hand causes the boron to become a hydrogen bonded zwitterionic species, which forms little to no N-B bond at all. [21]



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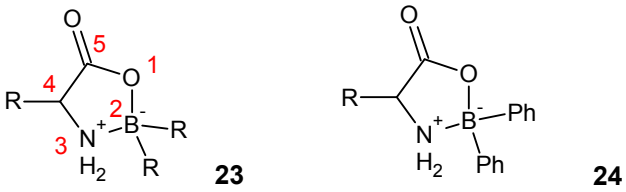
Picture 5: *Structure of o-(N,N-dialkyl aminomethyl)arylboronate **22** [21]*

The N-B bond energy can be studied by such methods as ^{11}B and ^{14}N NMR, dynamic NMR, theoretical calculations, microwave spectroscopy, electron diffraction crystallography and X-ray crystallography. The N-B bond length can be used to deduce the bond strength, and it varies from 1.57 Å to 2.91 Å. The geometry of a tetravalent boron changes from a tetrahedral to a trigonal planar, as the N-B bond gets weaker. [19]

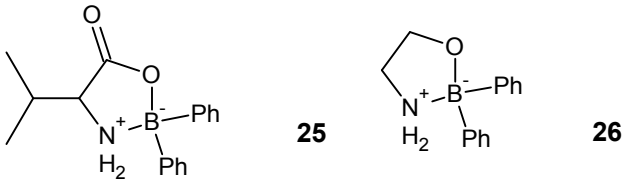
2.2.1 Boroxazolidones

Boroxazolidones are a subset of N-B bond-containing compounds. In addition to the previously mentioned potentials of boron and N-B bond compounds, boroxazolidones have interesting potentials of their own. A boroxazolidone-forming reaction can be used to protect the functional groups of an α-amino acid [22] or to turn sensitive alkyl- or aryl-substituted boron compounds to more stable solids [23]. Similar molecules, as focused on in this thesis, the 2,2-diphenyl-1,3λ^4,2λ^4,-oxazaborolidin-5-ones **24**, have been discovered to show cytotoxic activity against the cell lining of colon cancer and leukemia cells. [24] They can also be used for dyeing polymer fibers, in the Diels-Alder reaction and in other applications [25].



Picture 6: *The structure and ring numbering of a general boroxazolidone 1,3λ⁴,2λ⁴-oxazaborolidin-5-one **23**, and the structure of 2,2-diphenyl-1,3λ⁴,2λ⁴,-oxazaborolidin-5-one **24***

The naming of compounds similar to **24** differs from reference to reference. An (L)-valine-derived boroxazolidone with two phenyls at the boron (**25**) can be called L-valinatodiphenylboron [2] or 1,1-diphenylboroxazolidone derivate of (L)-valine [26]. One name for the boroxazolidone ring **23**, which is central to this thesis, is 1-oxa-3-azonia-2-boranuidacyclopentan-5-one [27]. Two other names for the same ring with 2 phenyls at the boron are 2,2-diphenyl-1,3-oxazaborolidin-5-one [24] and 2,2-diphenyl-1,3,2-oxazaborolidin-5-one [28]. For a similar molecule (**26**), the name 2-aminoethoxydiphenyl borate is used [29]. With this logic, compound **25** could be called 2-amino-3-methylbutanoic acid diphenyl borate. Another paper uses the name 2-aminoethyl diphenylborinate for the exactly same compound (**26**) [30].



Picture 7: *The structure of a (L)-valine-derived boroxazolidone **25** and 2-aminoethoxydiphenyl borate **26***

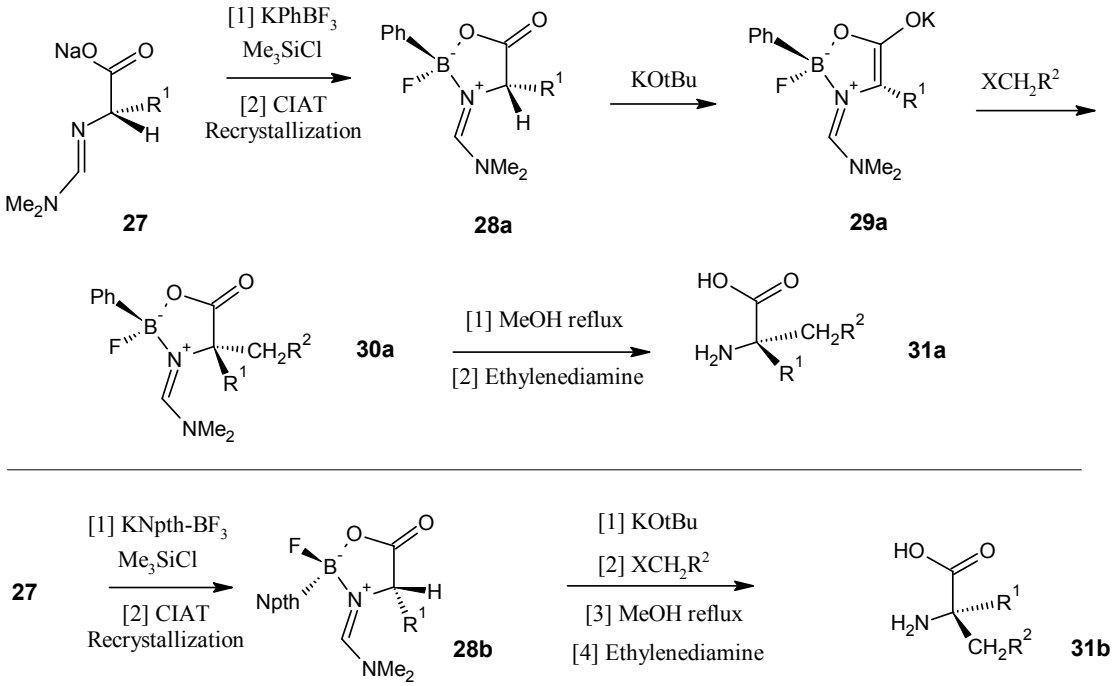
The most systematically accurate name for the ring of compound **23** is 1,3λ⁴,2λ⁴-oxazaborolidin-5-one. For heterocyclic compounds, the priority of naming is O>N>B and the prefixes are respectively *oxa, aza and bora* from which the last *a* can be removed. The suffix *-olidine* is used for fully saturated ring systems containing nitrogen and five atoms in the ring. The *e* from olidine can be removed and finally the suffix *-one* can be added to mark the carbonyl. [31; 32] The λ^n expression is used to indicate a non-standard valence of heteroatoms [33], so in this case, λ^4 means that the boron and nitrogen have a valence of four. Substituents are written before the ring's name in alphabetical order and prefixes such as *bis* or *tri* have no effect on the order [31]. For compound **25**, the systematic name is thus 4-isopropyl-2,2-diphenyl-1,3λ⁴,2λ⁴-oxazaborolidin-5-one. In this thesis, the more trivial name boroxazolidone will be used to refer to compounds, which contain the 1,3λ⁴,2λ⁴-oxazaborolidin-5-one **23** ring structure.

Because of the N-B bond, boroxazolidones are more stable to air and moisture than many other organoboron compounds [34]. The carbonyl group further stabilizes the

ring. 2-Aminoethoxydiphenyl borate **26** hydrolyzes easily to diphenylborinic acid, but this does not happen for the similar amino acid complexes like compound **25**. [30] When the boron is substituted with aryl groups, the boroxazolidone is more stable towards hydrolysis than when the boron is substituted with alkyl groups [22]. The alkyl group at the 4-position (R in compound **24**) can be important for the properties of the boroxazolidone. One study looking at boroxazolidone-induced apoptosis, found that the R-group of 2,2-diphenyl-1,3λ^4,2λ^4,-oxazaborolidin-5-one **24** has an effect on the cytotoxicity of the compounds. A glycine-derived boroxazolidone (R is H) was more cytotoxic than the (L)-valine-derived boroxazolidone. The heterocyclic ring is the biologically active moiety. [28]

There are many routes to make boroxazolidones. Reactions between 1,2- or 1,3-aminoalcohols and a boron reagent, which can be an alkyl- or arylborinic acid, dialkyl- or diarylborinic acid, boronate, borane or borane dimethyl sulfide, are the most common method for making boroxazolidones [25]. Another route is to use α-amino acids and trialkylboranes [35]. In this thesis, a reaction between an amino acid (L-valine) and a triethylammonium tetra-arylborate was used to produce the boroxazolidones.

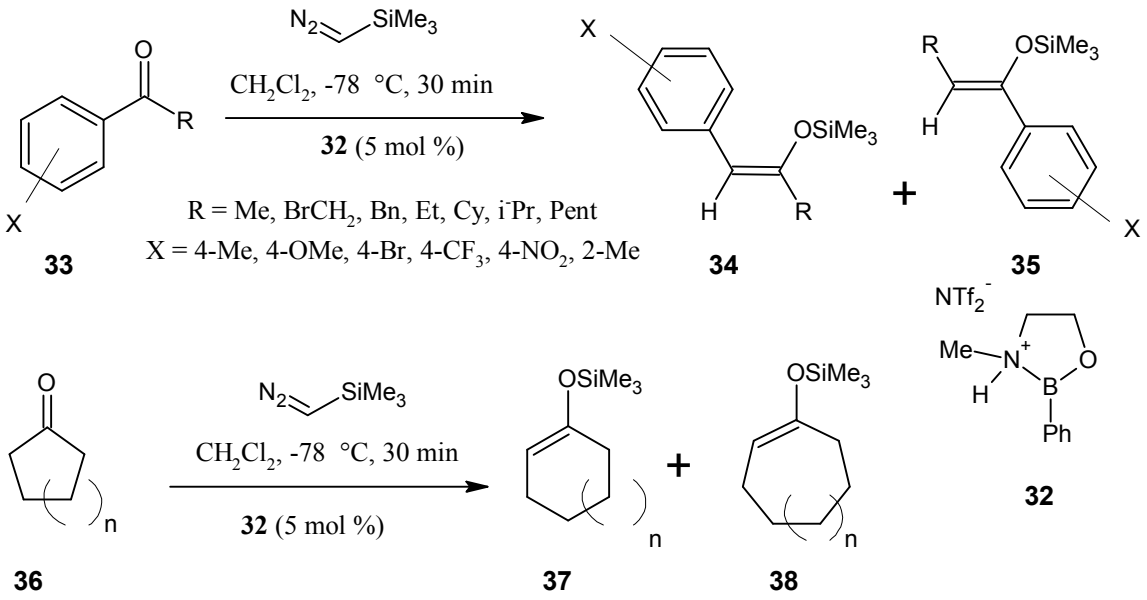
A boroxazolidone can be used to produce some chiral α-amino acids. One way to do this is by first forming a boroxazolidone from an α-amino acid-derived sodium amidino carboxylate **27** by using either potassium phenyltrifluoroborate and trimethylsilyl chloride or 1-naphthyltrifluoroborate and trimethylsilyl chloride. This boroxazolidone forms as two diastereomers where the configurations of fluorine and phenyl or naphthyl at boron are different but the product can be diastereomerically purified to **28a** or **28b** by using *crystallization-induced asymmetric transformation* (CIAT) and recrystallization, which can change the isomer from one to the other while it crystallizes. The phenyl and naphthyl-substituted compounds form the diastereomers with opposing absolute configuration in boron. This works the best for phenylalanine-derived compounds (R^1 is benzyl). The boroxazolidone can be reduced by KOtBu to **29**, and an alkyl halide can be used to add an alkyl group to the double bond to form **30**. This alkyl group's diastereomeric configuration is controlled by the position of the phenyl or naphthyl at boron so by either using **28a** or **28b**, one can choose the configuration of the alkyl group. The effect where a compound such as **29a**, which has no stereogenic center at the α-carbon, forms a stereocontrolled product, or in other words, retains stereochemical information, is called asymmetric memory. The boroxazolidone ring of **30** can then be broken with methanol reflux, and the imine can be removed by ethylenediamine to afford an enantiomerically highly pure α-amino acid **31a** or **31b**, which works the best when R^2 is $CH{=}CH_2$. [36] The 1-naphthyltrifluoroborate route has been shortened in scheme 4 to reduce repetition.



Scheme 4: *Boroxazolidone as an intermediate in the preparation of chiral α-amino acids from sodium amidino carboxylates*

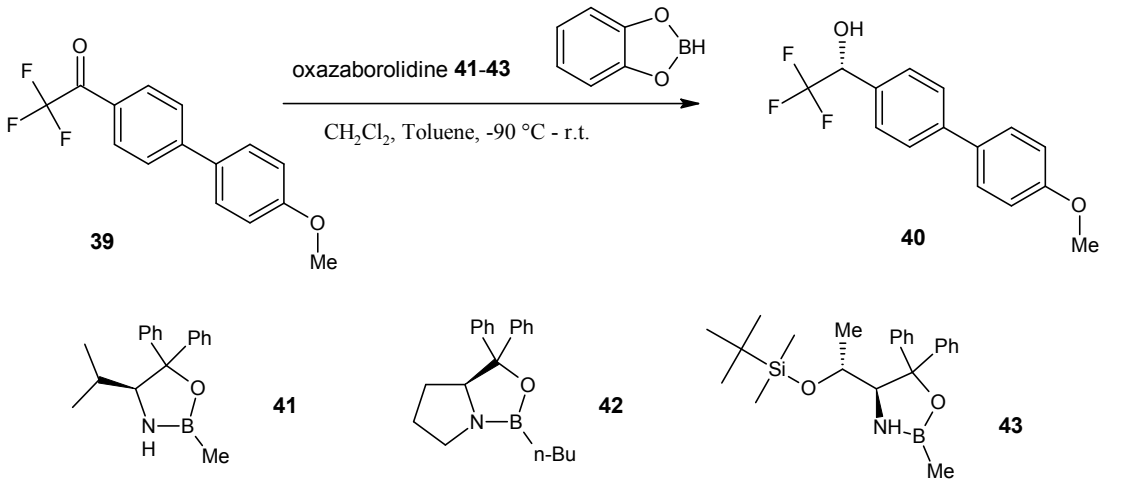
2-Aminoethoxydiphenyl borate **26** can modulate calcium signaling in the plasma membrane of cells. It can both inhibit and stimulate *store-operated calcium entry* depending on the concentration and the oligomeric state of the molecule. The N-B bond strength and the ring's strain together cause the multiple oligomeric forms, which can influence different binding sites in a cell membrane. [16] Controlling the intracellular Ca^{2+} concentration might be useful for treating heart disease and Alzheimer's disease [37].

Oxazaborolidinium ions containing monophenylboron and methyl-substituted quaternary nitrogen can catalyze homologation reactions of ketones to the corresponding silyl enol ether and ring expansion of cyclic ketones (scheme 5). Both reactions use trimethylsilyldiazomethane. [38] This oxazaborolidinium ion **32** is a Lewis acid and it catalyzes the reaction by activating the ketone. The oxazaborolidinium ion's bulkiness inhibits it from reacting with the product, which makes it better for this reaction than some other Lewis acids such as $ZrCl_4$. [39]



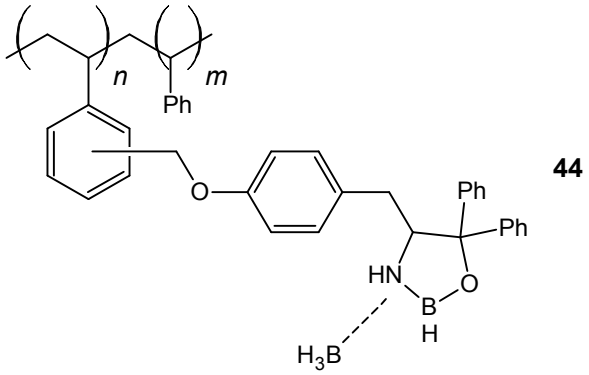
Scheme 5: *An oxazaborolidinium ion **32**, and the homologation of a ketone to silyl enol ethers and the ring expansion of a cyclic ketone catalyzed by **32** [39]*

Some prochiral ketones can be reduced to chiral secondary alcohols in good yields and ee values with catecholborane by using an oxazaborolidine as a catalyst. (L)-Threonine-derived, *t*-butyldimethylsilyl ether (TBDMSO) protected oxazaborolidine **43** showed the best result (95 % yield, 90 % ee, with 100 mol % of catalyst). Oxazaborolidines **41** and **42** were not quite as effective (95 % yield, 80 % ee and 93 % yield, 84 % ee respectively with 100 mol %). The higher effectiveness of **43** is attributed to the bulkiness of the TBDMSO group. [40]



Scheme 6: *Reduction of prochiral ketone 4-methoxy-4'-(trifluoroacetyl)biphenyl [40]*

Polymer-supported oxazaborolidines have shown good results for producing chiral alcohols from ketones by reduction with borane (BH_3). Turnover number of the catalyst was up to 560. [41]

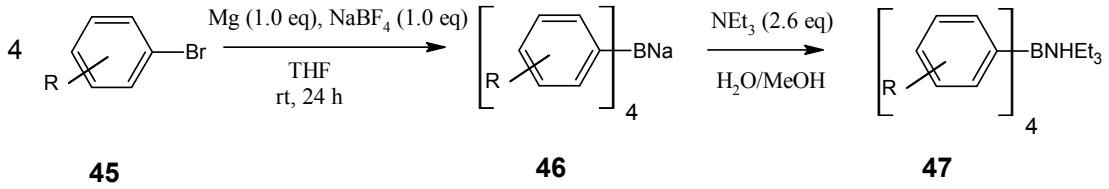


44

Picture 8: *A Polystyrene-supported oxazaborolidine **44** [41]*

2.3 **TEATABs**

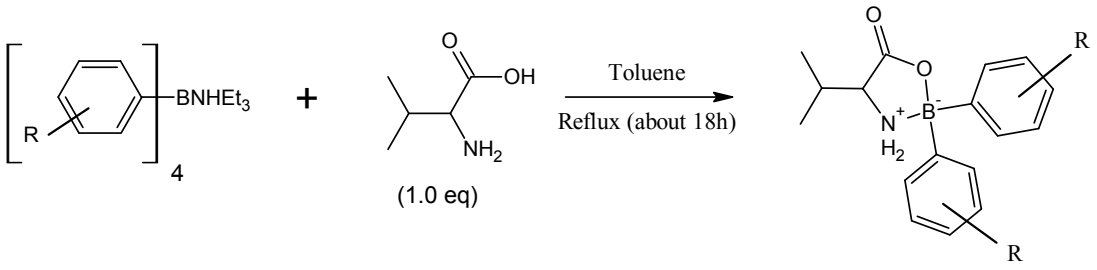
Triethylammonium tetra-arylborates (TEATABs) **47** were used for the boroxazolidone preparation because it had been shown that they could be made with different substituents in good yields, [12] and that they could be used to produce boroxazolidones [3] in good yields. TEATABs had been prepared in the lab before and were known to be stable compounds [12].



45 **46** **47**

Scheme 7: *The procedure for making TEATABs from various aryl halides by Kuuloja [12]*

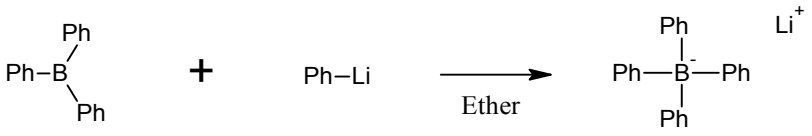
The first procedure for making a boroxazolidone in a similar manner to scheme 8 was developed by G. Baum already in 1970 but that reaction utilized sodium tetraphenylborate. [42] By changing the cation from sodium to triethylammonium, the solubility of the compound changes and its purification becomes easier. In addition to developing the method for making boroxazolidones from TEATABs, Kuuloja also studied the Suzuki reaction with the TEATABs as reagents and found that the cation affects the reactivity of the tetra-arylborate in that reaction. [12] Two aryl groups are lost as the corresponding benzenes in the reaction of scheme 8, so the atom economy of this reaction is not very high.



47 **48** **49**

Scheme 8: *The method for boroxazolidone synthesis from TEATABs and (L)-valine developed by Kuuloja [3]*

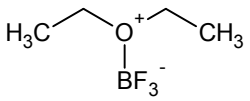
In this thesis, the TEATABs are used as reagents but tetra-arylborates can also be used in other ways. The first synthesized tetra-arylborate, tetraphenylborate, was used already in the 1940s to precipitate cations e.g. potassium, cesium or quaternary ammonium compounds. [43; 44] The tetraphenylborate was prepared from phenyllithium **51** and triphenylborane **50** in ether. [44]



50 **51** **52**

Scheme 9: *The synthesis of lithium tetraphenylborate* ***52*** *developed by Wittig et al. [44]*

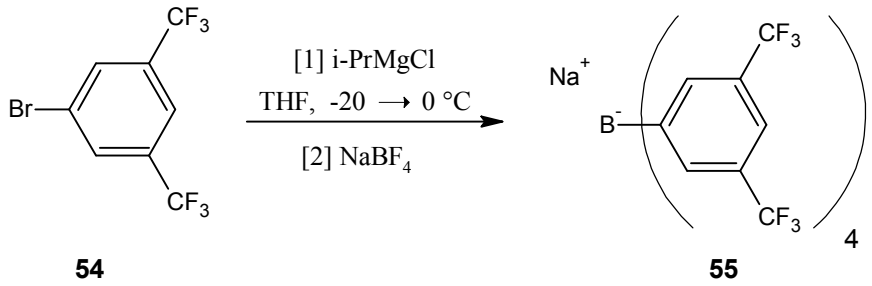
A more recent study found that tetra-arylborates with differing cations could be used to influence the selectivity of potentiometric ion sensors. This might give rise to a new family of charged carriers for cation-selective electrodes. Their method of synthesizing the tetra-arylborates was similar to that of Kuuloja but instead of adding $NaBF_4$ before forming the Grignard, they added boron trifluoride diethyl etherate **53** after forming the Grignard. [45]



53

Picture 9: *Boron trifluoride diethyl etherate*

If one deals with trifluoromethylphenyl Grignard reagents, it is important to know that these compounds might decompose in an exothermic explosion with excess magnesium metal [46]. A safe method for preparing sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate **55** utilizes isopropylmagnesium chloride (*i*-PrMgCl) instead of magnesium metal. [47]



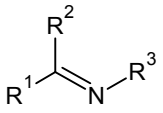
54 **55**

Scheme 10: *A safe method for preparing tetrakis[3,5-bis(trifluoromethyl)phenyl]borate [47]*

Fluorinated tetra-arylborates can be used to study very reactive cationic transition-metal complexes and have made it possible to use such cation complexes in polymerization and other applications. [47]

2.4 Imines

Imines contain a $R^1R^2C{=}NR^3$ moiety where the R groups can be hydrogens or alkyl or aryl groups. The R^3 can additionally be a metal or a metalloid (Si, Al, B, etc.) [48]. A subset of imines, in which R^3 is not H, is called Schiff bases. Two other subsets of imines are the aldimines and ketimines. In aldimines, R^1 or R^2 is a hydrogen atom and the other R is either an alkyl or an aryl group. In ketimines, both the R^1 and R^2 are alkyl or aryl groups. [49]



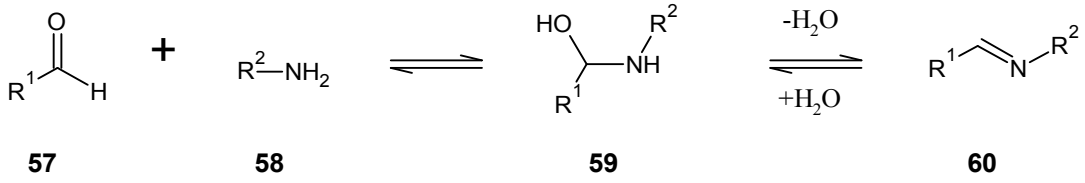
56

Picture 10: *Structure of a general imine* ***56*** *[49]*

Imines are important for many reactions. They can work as electrophiles in such reactions as reductions, additions and condensations. Some imines can coordinate to metals, and prochiral imines (R^1 is different from R^2) can be used to make chiral amines. [49] In nature, living organisms produce amino acids from keto acids and vice versa by a process called transamination, which involves an imine intermediate [48; 50]. Applications for imines in organic synthesis include addition reactions, Staudinger reactions, hetero Diels-Alder reactions and chiral Salen metal complex synthesis. Imines are present in many natural, semi-synthetic and synthetic compounds. [48]

Imines also have applications as medicines. They can have anticancer, antibacterial, antifungal, antiparasitic and antiviral activity or can be otherwise important as in the case of radionuclide complexes. Specific diseases, that imine-containing compounds have shown potential for treating, are malaria, carcinoma, tuberculosis and HIV. [48]

Imines can be made in multiple ways, such as condensation of an aldehyde or ketone with an amine, addition of aryl halides and liquid ammonia to aldehydes or ketones, hydroamination of alkynes, oxidative coupling of alcohols and amines, dehydrogenation of secondary amines, and coupling of aldehydes or ketones with nitro compounds. [49] This thesis focuses on the condensation between aldehydes and amines as the route for preparing the imines. Scheme 11 shows the general imine formation reaction from an aldehyde **57** and a primary amine **58**. The reaction starts by a nucleophilic attack of the nitrogen's lone pair electrons to the carbonyl carbon. Water elimination from the hemiaminal intermediate **59** is necessary for the imine **60** formation. Imines can revert to their starting materials via hydrolysis. Because of this, water must be removed from the reaction mixture in many cases to push the reaction to the right. This can be done by, for example, a Dean-Stark apparatus, molecular sieves or dehydrating agents. Lewis acids can catalyze the first step of the reaction, possibly by attaching to the carbonyl oxygen [51; 52]. Additionally, the Lewis acid can irreversibly bind to water in the later step. [49]



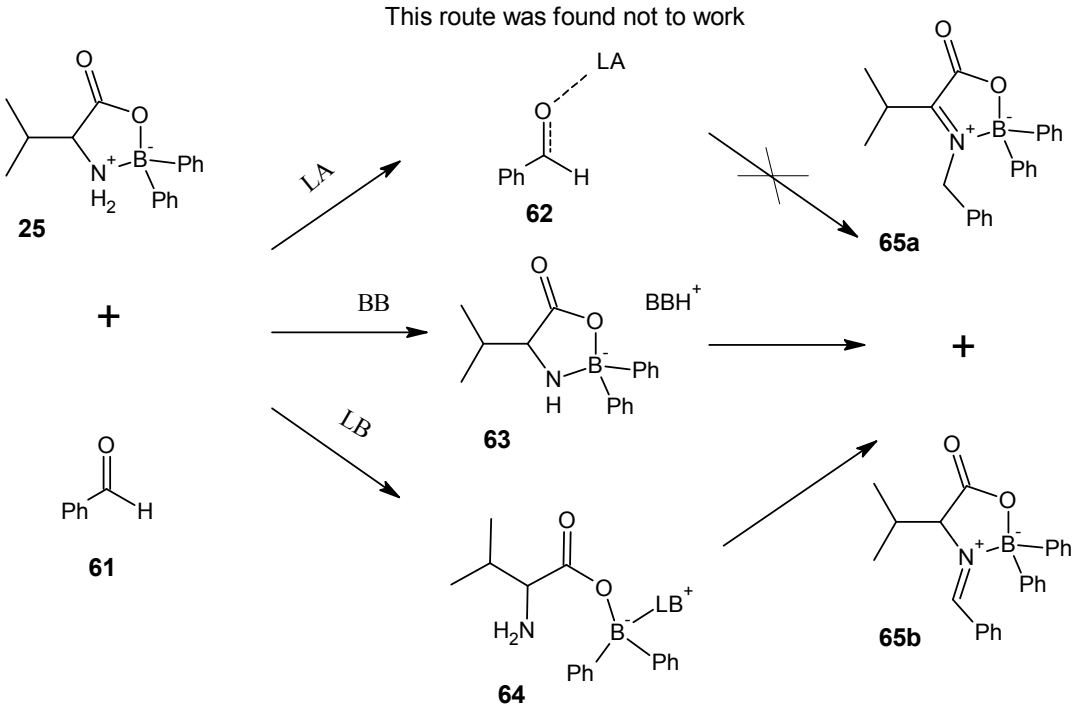
Scheme 11: *General imine formation from an aldehyde and a primary amine [49]*

Typically, imine formation happens most efficiently at pH 4-6 because a proton is needed for the water to leave but too much acidity will protonate the amine and prevent the reaction from starting. Usually, an imine must have an aromatic substituent at its double bond nitrogen or carbon, or it will decompose easily via hydrolysis. [50]

The imine condensation reaction between benzaldehyde **61** and boroxazolidone **25** has some unusual properties. Lewis acids are not effective for catalyzing it, and water removal from the reaction mixture is not necessary either because using molecular sieves made no difference when Mannoja tested it. A Lewis base (LB) was found to catalyze the imine formation between the boroxazolidone and benzaldehyde. [2] A Lewis base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or TBD can transfer electron density to an acceptor. Typically, this enhances the nucleophilicity of the acceptor but depending on the acceptor atom, this can instead enhance the electrophilicity of the acceptor. This means that Lewis bases can catalyze reactions of nucleophilic, electrophilic and ambiphilic reagents. [53]

In the reaction with a boroxazolidone, a Lewis base should attack the boron, break the N-B bond (compound **64**) and thus make the amine more likely to attack the aldehyde's carbonyl. Later, the LB should leave from the boron and the N-B bond should form again. Mannoja found that by changing the Lewis base, either the ketimine **65a** or the

aldimine **65b** could be produced. Nitrogen-containing Lewis bases like DBU produced the ketimine in the best yields. DBU is also a Brønsted base, which could mean that it deprotonates the amine (compound **63**) instead of attacking the boron, and catalyzes the reaction in this way. In the case of aldimine formation, phosphine-derived Lewis bases such as PPh_3 worked the best. This could mean that when a Lewis base attacks the boron and thus weakens or breaks the N-B bond, the aldimine is the favored product. On the other hand, if the Lewis base is also a Brønsted base, it can then isomerize the aldimine into the ketimine. Using five equivalents of benzaldehyde was found to produce the best yield, and it is more reasonable to use an excess of the aldehyde than an excess of boroxazolidone because the boroxazolidone is more valuable. The best solvent was found to be 1,2-dichloroethane (DCE) and a temperature of 80 °C. [2]



Scheme 12: *The possible routes of ketimine* ***65a*** *and aldimine* ***65b*** *formation from boroxazolidone* ***25*** *and benzaldehyde* ***61*** *via Lewis acid, Brønsted base and Lewis base catalysis as suggested by Mannoja [2]*

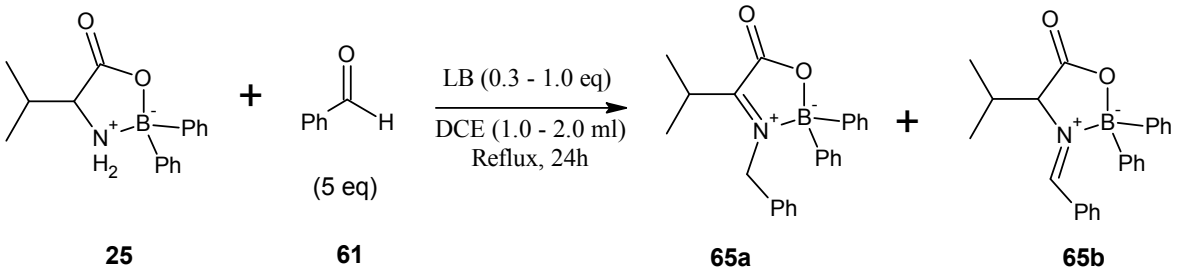
The nomenclature of the imines of this thesis is close to the boroxazolidones. The ketimine **65a** has an unsatured ring so the *-olidine* suffix changes to *-ole* [31], and the name *benzyl* is used to mark the $PhCH_2$- group [54]. Thus the name of **65a** becomes 3-benzyl-4-isopropyl-2,2-diphenyl-1,3λ^4,2λ^4-oxazaborol-5-one. For the aldimine **65b**, the ring remains saturated but the substituent PhCH= at nitrogen is called *benzylidene* [54] . Thus aldimine **65b** is systematically called 3-benzylidene-4-isopropyl-2,2-diphenyl-1,3λ^4,2λ^4-oxazaborolidin-5-one.

3. RESULTS AND DISCUSSION

This thesis' experiments were performed in the synthesis laboratory of the Department of Chemistry and Bioengineering in Tampere University of Technology during January 2016 - June 2016. The motivation for this thesis was to deepen the understanding about imine condensation between aldehydes and boroxazolidones and about the N-B bond. The first three subchapters 3.1, 3.2 and 3.3 contain the important results in regards to the motivation of the thesis, and the later subchapters describe the results obtained as a byproduct of the research. All successfully prepared imines were isolated by column chromatography. The measured ^{1}H and ^{13}C NMR spectra are explained for all prepared compounds but the peaks remaining nearly constant are mentioned only once for each group of compounds. The NMR explanations do not always cover the aromatic area because of its ambiguity. In ^{13}C NMR measurements, all C-H interactions were decoupled so these interactions do not produce multiplets.

3.1 Lewis base screening

Mannoja had already optimized the imine formation reaction of boroxazolidone **25** to a high degree. She had found a good solvent and the proper temperature. She had found that bases work as the catalyst instead of acids, and she had found the proper amounts of the aldehyde **61**, boroxazolidone **25**, catalyst and solvent to be used. She also found that bases, which are either Lewis bases or both Lewis and Brønsted bases produced the best results. [2] As there were still many untested LBs, more screenings were done to determine if some other LB than DBU could achieve a higher yield of the ketimine **65a** and if some new LB would yield the aldimine **65b**.



Scheme 13: *The reaction for Lewis base screening*

Scheme 13 shows the procedure for LB screening. Products were obtained as single isomers **65a** or **65b** as determined by ^{1}H NMR. If the isolated yield was too low, or the sample was known to be impure from thin-layer chromatography (TLC), ^{1}H NMR was not performed. The default order of addition of reagents was boroxazolidone and solvent first, then aldehyde and finally LB. The results are shown in table 2.

First, replicating the result of a 62 % yield of ketimine **65a** by Mannoja was attempted. This was found to be difficult. The reaction produced multiple product spots on TLC, and these products could not be easily separated by column chromatography. Adding DBU before benzaldehyde was also attempted (entry 2), as well as using 1.0 eq of DBU instead of 0.3 eq (entry 3). However, the yield only worsened, and the problem of multiple products remained. Finally, the best result was achieved by using freshly distilled DBU and 2 ml of DCE (entry 4). Even then, the yield (46 %) was clearly below that of Mannoja's (62 %). The amount of DCE was increased by 0.5 ml because the system was found to lose some solvent during reflux.

Then, other LBs were tested. Potassium *tert*-butoxide (*t*-BuOK) produced a pure ketimine **65a** but the yield was only 28 % (entry 5). 1,8-Bis(dimethylamino)naphthalene (proton sponge) produced a better yield of ketimine **65a** (53 %) than DBU, and the product was pure (entry 6). 2,4,6-Trimethylpyridine produced three product spots that were not isolated (entry 7). TBD was found to be the most effective LB for producing the ketimine **65a**, with a yield of 57 % (entry 8). After this, the amount of DCE and TBD was changed to see if the yield could be further improved but the yield worsened and two product spots were seen on TLC every time (entries 9 - 11). Using 0.3 eq of TBD and 2 ml of DCE remained as the best choice. This combination gave the best yield and only one product spot on TLC.

Sodium methoxide was found to produce the aldimine **65b**. Clear improvement was seen, when the amount of LB was increased from 0.3 to 1.0 eq (entries 12 and 13). The 48 % yield of aldimine **65b** with 1.0 eq of NaOMe is an estimate because the aldimine easily reverts to its starting materials, which can be seen in the ^{1}H NMR spectrum. Moving **65b** to a freezer under Ar right after purification might help to preserve it. An interesting detail is that bulky potassium *tert*-butoxide produced a ketimine but sodium methoxide produced an aldimine even though they are both alkoxide-bases.

Table 2: *Isolated yields of ketimine* ***65a*** *or aldimine* ***65b*** *from the reaction between benzaldehyde and boroxazolidone with different Lewis base, equivalents of bases and solvent volumes*

Entry	LB	LB eq.	Solvent volume (ml)	Isolated yield (%) **65a**	**65b**
1	DBU	0.3	1.5	~51[a]	-
2	DBU (before aldehyde)	0.3	1.5	~32[a]	-
3	DBU	1.0	1.5	~34[a]	-
4	DBU (distilled)	0.3	2.0	46	-
5	*t*-ButOK	0.3	2.0	28	-
6	Proton sponge	0.3	2.0	53	-
7	2,4,6-Trimethylpyridine	0.3	2.0	-	-
8	TBD	0.3	2.0	57	-
9	TBD	0.3	1.0	~41[a]	-
10	TBD	0.5	1.0	~20[a]	-
11	TBD	0.1	2	~9[a]	-
12	NaOMe	0.3	2	-	~18[b]
13	NaOMe	1	2	-	~48[b]

[a] ^{1}H NMR was not done because the yield was too low or because the product was not TLC pure after column. [b] Aldimine had partially reversed to boroxazolidone and benzaldehyde when ^{1}H NMR was measured so the product was not pure.

In conclusion, TBD was the best LB for ketimine formation and NaOMe for the aldimine formation. However, even with TBD, the result of a 62 % yield of ketimine **65a** reported by Mannoja was not reproducible in this work. Finally, the NMR spectra of compounds **25**, **65a** and **65b** are described. The following ^{13}C NMR discussion for compounds **25** and **65a** is based on Mannoja's measurements. In this thesis, ^{13}C NMR spectra were measured, and placed in the appendix section, for new compounds only.

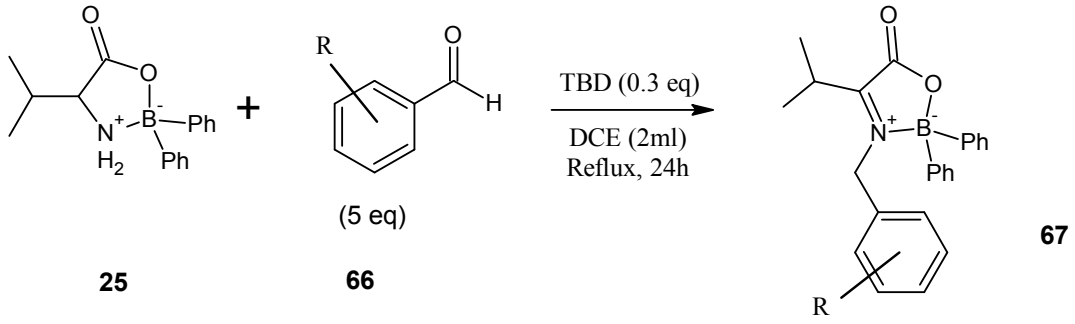
Boroxazolidone **25** has multiple characteristic ^{1}H NMR peaks in acetone-d_6. The two doublets at 1.03 (J=6 Hz) and 1.12 ppm (J=9 Hz) are from the isopropyl group's CH_3 moieties, the multiplet at 2.35 ppm comes from the isopropyl CH moiety and the multiplet at 3.71 ppm is from the 4-position CH moiety of the boroxazolidone ring. The small broad peaks at 5.7 and 6.7 ppm are from the NH_2 moiety. In ^{13}C NMR in DMSO-d_6, **25** shows two singlets at 19.02 and 19.46 ppm from the isopropyl CH_3 moieties, a singlet at 29.13 ppm from the isopropyl CH moiety, a singlet at 61.04 ppm from the ring 4-position carbon and a singlet at 174.09 ppm from the carbonyl carbon [2].

The characteristic ^{1}H NMR peaks for ketimine **65a** in $CDCl_3$ are a doublet at 1.25 ppm (J=9 Hz) from the isopropyl CH_3 moieties, a quintet at 2.99 ppm (J=6 Hz) from the isopropyl CH moiety and a singlet at 5.00 ppm from the benzyl CH_2 moiety. In ^{13}C NMR in $CDCl_3$, **65a** shows one singlet at 17.9 ppm from the isopropyl CH_3 moieties, a singlet at 30.20 ppm from the isopropyl CH, a singlet at 52.08 ppm from the benzyl CH_2, a singlet at 162.77 ppm from the heterocycle's 4-position carbon and a singlet at 175.78 ppm from the carbonyl carbon [2]. From comparing multiple ^{13}C spectra of

different ketimines, it seems that the three singlets at around 133.0, 128.35 and 128.15 ppm (in $CDCl_3$) correspond to the carbons of the phenyls bound to boron. This helps in assigning the rest of the peaks to other carbons. Most likely, the ^{13}C chemical shift of the phenyl carbon directly bound to boron, which would be the fourth peak, changes depending on the ketimine. For the aldimine **65b** in ^1H NMR in $CDCl_3$, the isopropyl CH_3 peaks are further apart than in boroxazolidone and produce two doublets at 0.66 (J=6 Hz) and 1.20 ppm (J=9 Hz). The most clear characteristic peak of the aldimine **65b** in $CDCl_3$ is the doublet at 8.88 ppm from the 4-position CH moiety of the ring.

3.2 Effect of different aldehydes on ketimine formation

Next, multiple aldehydes were screened with the newfound TBD to determine the effect of the aldehydes' substituents on ketimine formation.



Scheme 14: *The reaction for benzaldehyde screening*

From table 3, one can see that the halogen-containing benzaldehydes (entries 3, 4 and 7) produced a higher ketimine **67** yield than benzaldehyde (entry 1). This is most likely due to the electronegative halogen making the carbonyl more electrophilic and thus making it more susceptible to an attack from the amine. The other benzaldehydes containing electrophilic groups but not halogens (entries 6, 10 and 13), have clearly lower yields. The aldehydes substituted with less electrophilic groups (entries 5, 11 and 12) do not produce any product at all. Interestingly, 4-methoxybenzaldehyde produced a decent yield (entry 2) even though methoxy is an electron donating group.

Seeing that 4-trifluoromethylbenzaldehyde (entry 7) produced the best yield, its 3- and 2-configurations were also tested (entries 8 and 9). The 2-position should have the same electronic effect as the 4-position but the steric hindrance lowers the yield considerably. The 3-position has a lower electronic effect than the 4- and 2- positions so the lower yield is probably due to this effect.

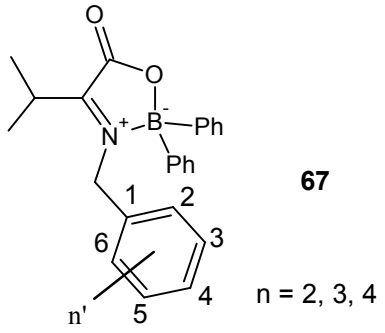
Table 3: *Yields of ketimines from reactions between different aldehydes and boroxazolidone with TBD as the base*

Entry	Product number	Aldehyde	Isolated yield (%)
1	**65a**	C_6H_5CHO	57
2	**67a**	4-$MeOC_6H_4CHO$	40
3	**67b**	4-BrC_6H_4CHO	61
4	**67c**	4-FC_6H_4CHO	60
5	**67d**	4-$NMe_2C_6H_4CHO$	-
6	**67e**	4-$NO_2C_6H_4CHO$	42[a]
7	**67f**	4-$CF_3C_6H_4CHO$	63
8	**67g**	3-$CF_3C_6H_4CHO$	52
9	**67h**	2-$CF_3C_6H_4CHO$	8
10	**67i**	4-CNC_6H_4CHO	35[a]
11	**67j**	2-HOC_6H_4CHO	-
12	**67k**	PhCH=CHO (*trans*)	-
13	**67l**	4-CO_2Me C_6H_4CHO	43[a]

[a] The aldehyde was dissolved in 1 ml of extra DCE prior to addition so the total solvent volume was 3 ml

When using a solid aldehyde, it can be beneficial to dissolve the aldehyde to 1 ml of DCE prior to adding it to the reaction mixture. In the case of entry 6, the yield increases from 18 to 42 % by using this procedure. However, for entry 10, this procedure only increases the yield from 31 to 35 %, and entry 3 had a high yield of 61 % even without this extra step. In conclusion, there is a correlation between the benzaldehyde's substituent being electron withdrawing and a good imine yield. It is easy to understand that electron withdrawing groups increase the yield but for some reason the effect of halogen groups is larger than the effect of other EDGs. In addition, 4-methoxybenzaldehyde does not fit into this correlation at all, as observed in entry 2.

All of the ketimines **67** successfully prepared have similar ^{1}H NMR and ^{13}C NMR peaks in $CDCl_3$ as the ketimine **65a** already detailed in the previous subchapter 3.1, with small variations in chemical shifts. Only the substituent R group changes in the spectra. For the fluorine-containing compounds, it is important to know that a carbon coupling with fluorines shows a multiplet in ^{13}C NMR because of ^{19}F. This means that getting a good quality ^{13}C NMR spectrum from those compounds requires more sample and more scans than usually. A carbon coupling to one fluorine atom shows a doublet and a carbon coupling to three fluorine atoms shows a quartet. The following picture 11 numbers the carbons of the ketimine's benzyl phenyl ring so that further discussion is unambiguous. To determine the positions, spectra of similar compounds were searched [55].



67

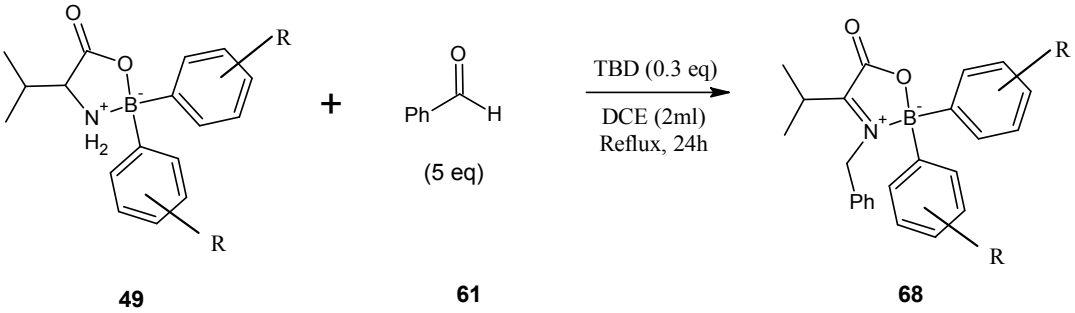
Picture 11: *Positions of carbons in the benzyl phenyl ring*

The following measurements were all performed in $CDCl_3$. **67a** shows a characteristic CH_3 moiety singlet from the methoxy at 3.71 ppm in ^1H NMR and at 55.5 ppm in ^{13}C NMR. **67b** shows no characteristic peaks. **67c** shows four characteristic doublets in ^{13}C NMR, resulting from coupling with one fluorine, 162.53 ppm (J=247.5 Hz) from 4-position, 129.64 ppm (J=3.75 Hz) from 1-position, 129.24 ppm (J=7.5 Hz) from 2- and 6-positions and 116.20 ppm (J=22.5 Hz) from 3- and 5-positions. **65e** shows no clear characteristic ^1H or ^{13}C peaks but the carbon of the benzene ring connected to the nitro group does shift to lower field, and it is at 147.76 ppm in ^{13}C. **65f** shows three characteristic ^{13}C quartets from coupling with three fluorines, 130.77 ppm (J=33 Hz) from 4-position, 126.05 ppm (J=3.8 Hz) from 3- and 5-positions and 123.79 (J=271 Hz) from the CF_3 moiety. Finding the quartets resulting from coupling with three fluorines of the trifluoromethyl can be difficult. Especially the trifluoromethyl moiety's carbon peaks can be very small even with a large amount of sample and a high number of scans. **65g** and **65h** have the same kind of characteristic peak systems as **65f** in ^{13}C but they show only nine peak systems instead of the expected eleven. The CF_3 moiety quartet for **65g** and **65h** cannot be found. The quartet is most likely hidden in the background noise because the amount of sample was too small. **65g** shows quartets at 131.71 ppm (J=33.7 Hz) from the 3-position, at 125.44 ppm (J=3.7 Hz) from the 2- or 4-position and at 123.93 ppm (J=4.0 Hz) from the 2- or 4-position. One singlet of the **65g**'s 1-, 6- or 5-position is overlapping something else. **65h** shows quartets at 131.90 ppm (J=1.5 Hz) from the 1- or 3-position and at 126.47 ppm (J=6 Hz) from the 1- or 3-position. The 2-position quartet and one singlet from the 4-, 5- or 6-position cannot be found. The quartet is most likely too small and the singlet overlaps something else. **65i** shows a singlet in ^{13}C NMR for the cyano group probably at 118.03 ppm. **65l** has a characteristic ^1H NMR singlet at 3.87 ppm from the carboxylate methyl moiety and two characteristic ^{13}C NMR singlets from the carbonyl of the carboxylate at 166.35 ppm and from the carboxylate methyl at 52.48 ppm.

3.3 Effect of different boroxazolidones on ketimine formation

Then, forming ketimines from four additional boroxazolidones with benzaldehyde and TBD was tested. The substituents of the boron should affect the N-B bond, and thus the

amine, and finally the ketimine formation. Of all of these boroxazolidones, only the 2,4-difluoro-substituted **49d** dissolves easily into DCE whereas the others need warming and still do not dissolve completely.



Scheme 15: *The reaction for boroxazolidone screening*

One could expect that electron donating groups in the phenyl rings of **49** would reduce the Lewis basicity of the boron and thus weaken the N-B bond. As the N-B bond weakens, the nucleophilicity of the nitrogen should increase and the yield from imine condensation should increase as well. However, the results seen in table 4 from these reactions do not support this idea. The difference between the phenylboron having electron-withdrawing fluoro groups (entry 5) or an electron-donating methyl group (entries 2 and 3) is very small. When the phenylboron is substituted with the most electron donating group in this series, methoxy, the yield clearly decreases (entry 4). A side product forms in entry 4, unlike in other imine formation reactions done with TBD as the base. A side product always lowers the yield in these reactions.

Table 4: *Yields of ketimines from reactions between benzaldehyde and different boroxazolidones with TBD as the base*

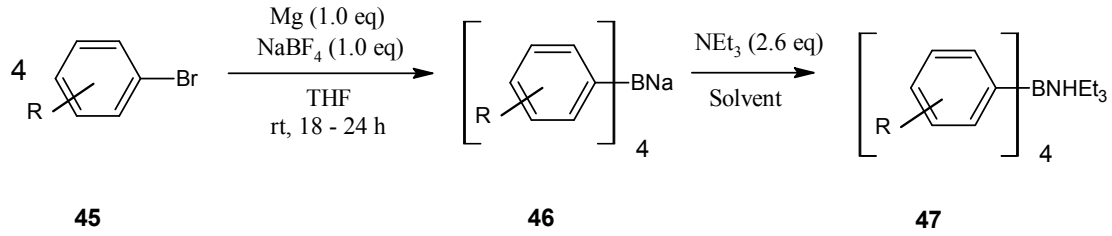
Entry	Product number	R	Isolated yield (%)
1	**65a**	H	57
2	**68a**	4-Me	48
3	**68b**	3-Me	60
4	**68c**	4-MeO	29
5	**68d**	2,4-F	52

The following measurements were performed in $CDCl_3$. **68a** has a characteristic methyl moiety singlet at 2.35 ppm in ^1H NMR and at 21.51 ppm in ^{13}C NMR. **68b** also has a characteristic methyl moiety singlet at 2.32 ppm in ^1H NMR at 21.91 ppm, in ^{13}C NMR. **68b**'s ^{13}C spectrum has two overlapping aryl carbon singlets. **68c** has a characteristic methoxy moiety singlet at 3.81 ppm in ^1H NMR. In ^{13}C NMR, **68c** has a methoxy singlet at 55.32 ppm and a singlet from an aryl carbon bound to the methoxy at 159.67 ppm. **68d** has four characteristic doublets of doublets in ^{13}C NMR from C-F coupling, at 166.55 (J=168.0, 12.8 Hz), 163.30 (J=174.4, 12.4 Hz), 111.65 (J=19.1, 3.4 Hz) and 103.40 ppm (J=30.0, 24.0 Hz). Of these, the first two correspond to the carbons bound to fluorines and the last two most likely correspond to the meta-positions of which the

second one (103.40 ppm) is the carbon between the carbons bound to fluorine. The multiplet at 136.69 - 137.24 ppm most likely contains the peaks from the remaining two carbons of the borophenyl. The ^{13}C NMR of **68d** shows three peaks for the benzyl CH_2 moiety at 52.0 ppm but there should be just one singlet. This might be due to the fluorines coupling with this carbon.

3.4 TEATABs

Multiple different TEATABs were made to be used for preparing the corresponding boroxazolidones. Scheme 16 shows the procedure for TEATAB synthesis developed by Kuuloja.



45 **46** **47**

Scheme 16: *General procedure for TEATAB synthesis*

Table 5 shows the yields of different TEATABs. It is difficult to say, which aryl bromide is the best for this reaction, because the TEATAB yield depends on the solubility difference between the sodium tetra-arylborate (NaTAB) and the corresponding TEATAB. All of the successful reactions consumed all or almost all of the magnesium flakes so the Grignard formation should not be the limiting step in any of these yields.

The tetraphenylborate of entry 1 seems to have the largest solubility difference between its sodium and triethylammonium salts in a 1:1 water/methanol solvent system because it precipitates so easily and thus produces a very high yield, once triethylamine is added. The low yield from entry 2 is due to using too much solvent when the reaction was scaled up from Kuuloja's paper. Increasing the yield of entry 2 was attempted by adding pure triethylamine to the filtrate after filtering out the precipitated solid. More solid did form into the solution but it was not pure. Generally, it seems that to get a pure product in good yield, one must be careful not to use too much solvent in the last step and just filter out any insoluble material before adding triethylamine. If the product does not precipitate, a refrigerator or a freezer can be used. Removing solvent by evaporation, which mostly removes the methanol, could help precipitate the TEATAB but it might also produce an impure mixture because the NaTAB might also precipitate.

Table 5: *Yields and used solvent systems for TEATABs*

Entry	Product number	R	Solvent	Isolated yield (%)
1	**47a**	H	1:1 H_2O/MeOH	95[a]
2	**47b**	4-MeO	1:1 H_2O/MeOH	13
3	**47c**	4-Me	1:1 H_2O/MeOH	66
4	**47d**	3-Me	1:1 H_2O/MeOH	67
5	**47e**	2,4-F	2:1 CH_3CN/MeOH	-
6		2,4-F	1:1 H_2O/MeOH	46
7	**47f**	4-CN	-	-
8		4-CN	-	-
9	**47g**	4-F_3CSO_3	First 1:1 H_2O/MeOH Then 2:1 H_2O/THF	-
10		4- F_3CSO_3	First MeOH Then Et_3N Then H_2O	-

[a] Prepared from commercial sodium tetraphenylborate, not from bromobenzene

Attempts to start the Grignard reaction with 4-bromobenzonitrile (entry 7) failed. Literature was searched and an alternative method [56] was found that used a lower temperature and diethyl ether instead of THF (entry 8) but it did not work either. This alternative method also had a problematic issue with the solubility of 4-bromobenzonitrile to diethyl ether, and it seemed that the authors had possibly made a mistake with either the amount of diethyl ether or bromobenzonitrile. Activating the Mg was also attempted for entry 8 by grinding it under Ar to a fine powder. The Grignard reaction for the 4-bromobenzotriflate worked but the final TEATAB **47g** did not precipitate. The mixture did not dissolve into a water/methanol mixture almost at all (entry 9) so using only methanol, then adding triethylamine, and finally adding water was attempted (entry 10). Some precipitation was achieved in entry 10 and a small amount of solid was removed with a centrifuge but it was not pure in ^{1}H NMR. The spectrum suggests a mixture of tetra- and triarylborate.

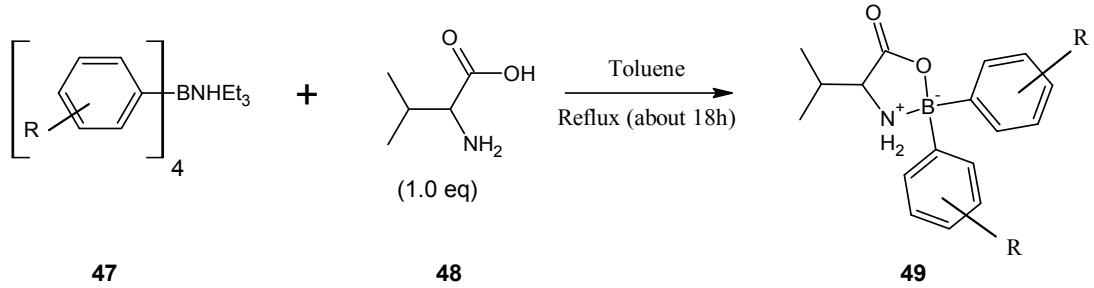
TEATAB NMR measurements were performed in acetone-d_6 because of their higher solubility to it than to chloroform. All of the TEATABs except **47a** have a characteristic triplet in ^{1}H NMR at around 1.4 ppm corresponding to the triethylammonium's CH_3 moiety and a quartet at around 3.4 ppm corresponding to the triethylammonium's CH_2 moiety. For **47a**, these peaks are broad but they have the same integrals and are at the same positions. In ^{13}C NMR, all TEATABs have two singlets at around 9 and 48 ppm, corresponding to the triethylammonium's CH_3 and CH_2 moieties, respectively. **47b** has a characteristic methoxy CH_3 moiety singlet at 3.66 ppm in ^{1}H NMR and at 54.87 ppm in ^{13}C NMR. The ^{13}C NMR information for **47a** and **47b** is from Kuuloja's measurements [12]. **47c** and **47d** both have characteristic CH_3 methyl moiety singlets at

2.17 and 2.13 ppm in ^{1}H NMR and at 20.65 and 21.60 ppm in ^{13}C NMR, respectively. Unlike in boroxazolidones and ketimines, ^{11}B causes some phenyl carbons to show quartets in ^{13}C NMR for all the TEATABs. For **47c** and **47d**, the quartet corresponding to the carbon bound to boron is at 161.17 (J=49.0 Hz) and 164.52 ppm (J=49.0 Hz), respectively. For **47c** and **47d**, the other phenyl carbons except the para-position also show quartets.

For **47e**, the carbons bound to the fluorines do not show a quartet from the boron but instead they just show doublets of doublets at 166.12 ppm (J=240.8, 10.5 Hz) and at 160.93 (J=237.0, 12.8 Hz) from the fluorine coupling. Three other carbons show coupling with boron and fluorine which forms doublets of quartets at 108.20 ppm (J=15.0, 3.3 Hz), 101.31 ppm (J=22.9, 1.6 Hz) and 100.89 ppm (J=23.3, 1.5 Hz). One could even expect to see doublets of doublets of quartets from a carbon coupling with two fluorines and one boron but such systems are not visible. The area at 137.66 - 137.98 ppm probably shows the peak systems for two carbons.

3.5 Boroxazolidones

The TEATABs **47** and (L)-valine **48** were used to produce different boroxazolidones. Scheme 17 shows the boroxazolidone formation reaction developed by Kuuloja.



Scheme 17: *General procedure for boroxazolidone synthesis*

This reaction has the same sort of problem as the TEATAB synthesis in that a good yield and ease of isolation of product depend on the low solubility of the boroxazolidone to the solvent (toluene). The non-substituted boroxazolidone **25** clearly had the lowest solubility in toluene and its purification was very easy. **49b** also precipitated rather quickly from the toluene but more slowly than **25**. **49a** had to be placed in a freezer to induce crystallization, and **49c** had to be recrystallized from toluene and placed in a freezer before any solid could be filtered out. As precipitation becomes harder to achieve, also the yield drops. Finally, **49d** does not precipitate even after recrystallization and being kept in a freezer for multiple days. Because of this, **49d** had to be purified by column chromatography, resulting in isolation of the desired product in reasonably good 73 % yield.

Table 6: *Yields of different boroxazolidones*

Entry	Product number	R	Isolated yields (%)
1	**25**	H	95
2	**49a**	4-Me	78
3	**49b**	3-Me	85
4	**49c**	4-MeO	47
5	**49d**	2,4-F	73[a]

[a] Column chromatography was needed for purification.

49d is also different from the other boroxazolidones, in that, once evaporated to dry, it forms an oily substance instead of a crystalline solid like almost all the other chemicals prepared in this thesis. However, once **49d** is sufficiently dry after days in a desiccator, the oily substance breaks down into a powder.

Characteristic NMR for **25** was already explained in the Lewis base screening subchapter 3.1, and the peaks stay nearly the same for all boroxazolidones except for the substituent at phenylboron. The following ^{1}H measurements are in acetone-d_6 and ^{13}C measurements are in DMSO-d_6, unless otherwise stated. For ^{1}H NMR, acetone is favorable to DMSO because it does not overlap with any peaks. DMSO is better for ^{13}C NMR because some boroxazolidones have better solubility to DMSO than to acetone and because DMSO does not overlap with any peaks in ^{13}C NMR. The ^{13}C NMR measurements for all boroxazolidones are different from the corresponding ketimines' measurements. In ketimines, the isopropyl CH_3 moieties and the phenyls at boron are symmetrical so the carbons at equal positions show only one singlet However, for the boroxazolidones, both the isopropyl CH_3 moieties and the phenyls connected to the boron are asymmetrical. For **49a**, also the methyl CH_3 moieties at the phenyls are asymmetrical. Compounds **49a**, **49b** and **49c** do not have any substituents, which might couple with the carbons. These ^{13}C peak systems of the boroxazolidones show up as pairs, which are close to each other. The term "pair", as used here, does not imply multiplicity like the term "doublet" would. These pairs only make sense if they are from carbons with the same positions.

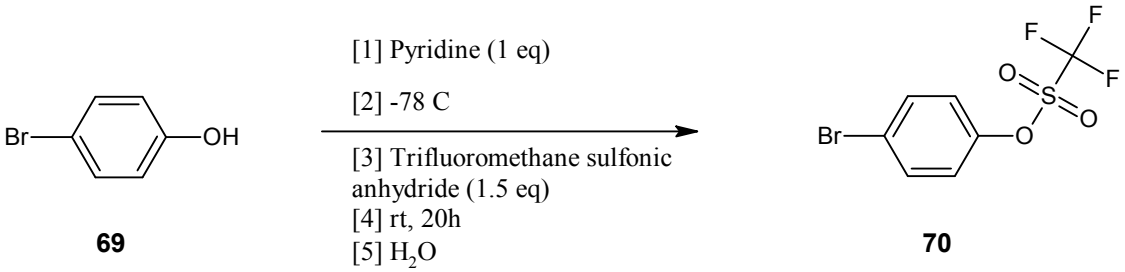
49a and **49b** show a characteristic methyl CH_3 moiety singlet at 2.25 ppm in ^{1}H NMR. In ^{13}C NMR, **49a** shows a pair of singlets at 21.57 and 21.53 ppm but **49b** shows just one singlet at 22.10 ppm, corresponding to the methyl moiety. **49c** has a characteristic methoxy CH_3 moiety singlet at 3.74 ppm in ^{1}H NMR and at 55.38 ppm in ^{13}C NMR. Boroxazolidones **25, 49a, 49b and 49c** have two singlets at around 19.4 and 19.0 ppm in ^{13}C NMR, corresponding to both of the isopropyl CH_3 moieties. For **49d**, these singlets are at 18.19 and 17.26 ppm. **49a** should show four pairs of singlets in the aromatic area but it shows only three pairs. The fourth pair is probably overlapping the other three. **49b** shows five pairs of singlets but it should have six pairs so the sixth is probably overlapping with the others. **49c** has three pairs of singlets of which the pair at 158.61 and 158.60 ppm is the phenyl carbon bound to the methoxy. This leaves just two

pairs of singlets, instead of the expected three pairs, to account for the other carbons so one of the pairs must again overlap the others.

49d's ^{13}C spectrum (in acetone-d_6) has multiple differences to the other boroxazolidones' ^{13}C spectra. It shows two peaks at 17.26 (one isopropyl CH_3 moiety) and 60.75 ppm (heterocycle 4-position) instead of the expected one peak for each. This cannot be about asymmetry and happens due to something else. The isopropyl CH moiety singlet is under the acetone peaks, which are at 28.5 - 30.0 ppm. The fluorine-substituted phenyl carbons produce doublets of doublets just like in the case of **49c** but this time there are pairs of doublets of doublets from both phenyls at 166.21 (J=196.1, 11.6 Hz), 166.18 (J=195.0, 12.0 Hz), 162.99 (J=200.6, 11.6 Hz) and 162.95 ppm (J=199.1, 12.4 Hz). One of the phenyl carbon positions forms a pair of triplets at 110.78 (J=3.8 Hz) and 110.53 ppm (J=3.4 Hz) instead of the expected pair of doublets of doublets. Another phenyl carbon produces the expected pair of doublets of doublets at 102.68 (J=29.6, 24.4 Hz) and 102.65 ppm (J=29.3, 24.8 Hz). Unlike with **49a**, **49b** and **49c**, **49d**'s spectrum shows all the peak systems for all benzene carbons.

3.6 Other results

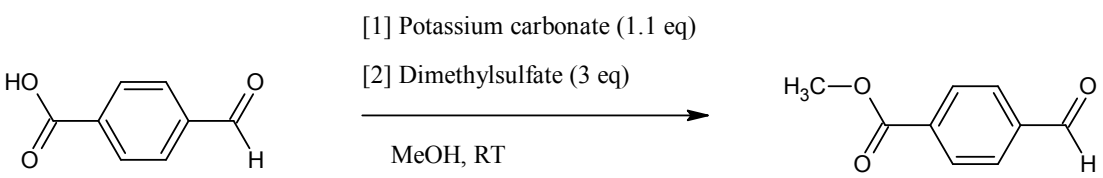
4-Bromobenzotriflate **70** was prepared in 90% yield for making the corresponding TEATAB. Scheme 18 shows the procedure used [57].



Scheme 18: *4-Bromobenzotriflate **70** preparation [57]*

Trifluoromethane sulfonic anhydride is very reactive and produces hydrogen fluoride gas so one should be extra careful with this reaction. The product shows a characteristic CF_3 moiety quartet in ^{13}C NMR at 118.91 (J=319 Hz) in $CDCl_3$.

4-Carboxybenzaldehyde **71** was protected to methyl benzaldehyde-4-carboxylate **72** in a 75 % yield to be used in the corresponding imine condensation (table 3, entry 13).



71 **72**

Scheme 19: *Protection of 4-carboxybenzaldehyde's carboxyl group*

It was surprisingly difficult to get this one pure because it easily produced two product spots or then some dimethyl sulfate or its degradation products stayed in the product regardless of washes. The product has a characteristic CH_3 moiety singlet in ^1H NMR at 3.96 ppm in $CDCl_3$.

4. EXPERIMENTAL

All reagents, except those prepared in the lab and described in this paper, and solvents were obtained from Sigma-Aldrich, Aldrich, Fluka, Merck or Tokyo Chemical Industries. All reagents and solvents were used as is unless otherwise stated. Reagent purity was generally > 95 %. All water used was milli-Q. All glassware was rinsed with acetone and dried in an oven or with a heat gun prior to the reactions.

TLC was performed to follow the reactions. The plates were aluminum pre-coated with silica gel (Merck TLC silica gel 60 F_{254}). Detection was done primarily with UV light. Staining was sometimes done with cerium molybdate for general detection and with ninhydrin for detecting amines (boroxazolidones). Column chromatography was performed on Merck silica gel 60 (0.040 - 0.063 mm).

All compounds were characterized by ^{1}H NMR to assess their structure and purity. ^{13}C NMR spectra of all new compounds were also recorded. Used solvents were $CDCl_3$, DMSO-d_6 and acetone-d_6. The used machinery is a Varian Mercury 300 MHz spectrometer. The internal standard for chemical shift δ (ppm) reference was trimethylsilane. All mentions of just *ether* mean diethyl ether.

4.1 TEATAB preparation

A paper from Kuuloja et al. [12] was used as the basis for all TEATAB preparations. Grignard reactions were always performed under Ar and with dried solvents. Mg flakes were not activated in any way beforehand. Flakes are preferable to powdered Mg because one can see the color changes inside the flask i.e. when the reaction starts. As usually, the Grignard reactions should be started carefully as not to cause too much boiling.

The THF used for the Grignard reaction was dried in the following way: First, it was pre-dried by stirring with NaOH overnight and distilled over the NaOH. Then, sodium flakes were added to the distilled THF, the system was refluxed, benzophenone was added, the system was refluxed some more and a blue color emerged. Ether was dried over sodium in presence of benzophenone as indicator.

4.1.1 Triethylammonium tetraphenylborate (47a)

11g (32 mmol, 1.0 eq) of commercial sodium tetraphenylborate was dissolved to 100 ml of MeOH/water (1:1). After the $NaBPh_4$ had dissolved, 200 ml of aqueous 2.5 wt%

solution of triethylamine (1.5 eq) was added dropwise while stirring. The solution changed to white and milky, and it was stirred overnight. After 20 h, the solid was filtered and washed with 3 x 20 ml of water. The product was dried in high vacuum. White powder (12.77 g, 95 % yield); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 7.35 (d, J=3 Hz, 8H), 6.94 (t, J=7.5 Hz, 8H), 6.77 - 6.81 (m, 4H), 3.36 (br. s., 6H), 1.35 (br. s., 9H). Appendix 1. Spectrum corresponds to Kuuloja's spectrum [12].

4.1.2 Triethylammonium tetra(4-methoxyphenyl)borate (47b)

In addition to the paper of Kuuloja et al. [12], a lab book note NK-629 was used to determine the best procedure. 3.59 g (147.7 mmol, 2.0 eq) of Mg turnings, an iodine crystal and 9 ml of THF (did not turn blue but should have been dry) were added to a 2-neck flask. 18.5 ml (147.7 mmol, 2.0 eq) of 1-bromo-4-methoxybenzene was mixed with 30 ml of THF in a dropping funnel. The flask was lowered to an oil bath to help initiate the Grignard formation. 1/10 of the 1-bromo-4-methoxybenzene solution was added dropwise. Boiling started, and the rest of the solution was added slowly. Oil bath temperature was around 75 ºC. After 4 hours, the flask was raised to cool, and 2.02 g (18.5 mmol, 1.0 eq) of sodium tetrafluoroborate was added by quickly raising the condenser and pouring it in. The system was stirred overnight at room temperature for 21 h.

The solution was quenched into 880 ml of 4:1:200 Na_2CO_3/NaOH/water solution while stirring. The solution was saturated with NaCl and extracted with 2 x 100 ml and 3 x 50 ml of ether. The ether was washed with brine (saturated aqueous sodium chloride solution) and evaporated. The solid was dissolved to 500 ml of 1:1 MeOH/water solution and filtered twice through celite. 200 ml of MeOH was added to get a clear solution. 230 ml of 2.5 wt% triethylamine (3.0 eq) solution was added. The solution was stirred overnight. No solid formed. Some solvent was evaporated in a rotavaporator. Precipitate formed, and it was filtered and washed with water and hexane. White solid (1.36 g, 13 % yield); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 7.17 - 7.22 (m, 8H), 6.52 - 6.57 (m, 8H), 3.66 (s, 12H), 3.42 (quar, J=9 Hz, 6H), 1.38 (t, J= 7.5 Hz, 9H). Appendix 2.

4.1.3 Triethylammonium tetra(4-methylphenyl)borate (47c)

THF was the same as used with **47b**. 2.878 g (26.2 mmol, 1.0 eq) of sodium tetrafluoroborate, 2.552 g (104.7 mmol, 1.0 eq) of Mg turnings, an iodine crystal and 6 ml of THF were set to a flask. 18.24 g (104.7 mmol, 1.0 eq) of 4-bromotoluene was mixed with 58 ml of THF and set to dropping funnel. The flask was lowered to a 75 ºC oil bath, and the bromotoluene solution was slowly added. Vigorous boiling began after half of the solution had been added. The solution was refluxed for 1 h, and it was left to stir at room temperature for 16 h. The reaction mixture was quenched to 70 ml of

4:1:200 Na_2CO_3/NaOH/water solution while stirring. The THF layer was removed. The water layer was saturated with NaCl and extracted with 4 x 60 ml of ether. The ether and THF are combined and washed with 100 ml of brine. The organic layer was evaporated, and the resulting solid was dissolved to 300 ml of MeOH/water solution. The solution was filtered through celite to get a clear solution. 70 ml of 10 wt% aqueous triethylamine (68.1 mmol, 2.6 eq) solution, with 10 ml of MeOH to avoid separation of the triethylamine and water into layers, was added slowly to the solution. A white precipitate formed, and the solution was stirred for 2.5 h. The solid was filtered and washed with hexane and water. White solid (8.3 g, 66 % yield); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 7.20 - 7.25 (m, 8H), 6.74 (d, J=9 Hz, 8H), 3.32 (quar, J=7.0 Hz, 6H), 2.17 (s, 12H), 1.33 (t, J=7.5 Hz, 9H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm): 161.17 (quar, J=49.0 Hz), 136.37 (quar, J=1.5 Hz), 129.37 (s), 126.14 (quar, J=2.8 Hz), 47.38 (s), 20.65 (s), 8.79 (s). Appendices 3, 4a and 4b.

4.1.4 Triethylammonium tetra(3-methylphenyl)borate (47d)

2.549 g (104.7 mmol, 1.0 eq) of Mg turnings, 2.881 g (26.2 mmol, 1.0 eq) of sodium tetrafluoroborate, an iodine crystal and 6 ml of THF were added to a flask. 12.7 ml (104.7 mmol, 1.0 eq) of 3-bromotoluene was dissolved to 58 ml of THF in a dropping funnel. 1/5 of the bromotoluene solution was added to the solution, and boiling started already even though the oil bath's temperature was only 30 ºC. The oil bath was removed, and the rest of the solution was added at a suitable pace to keep the boiling going. Left to stir at room temperature for 18 h. The rest of the procedure goes just like with **47c**. White solid (8.37 g, 67 % yield); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 7.21 - 7.23 (m, 4H), 7.13 - 7.18 (m, 4H), 6.82 (t, J=7.5 Hz, 4H), 6.60 (d, J=6 Hz, 4H), 3.32 (quar, J=7.0 Hz, 6H), 2.13 (s, 12H), 1.33 (t, J=7.5 Hz, 9H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm): 164.52 (quar, J=49.0 Hz), 137.16 (quar, J=1.5 Hz), 133.76 (quar, J=1.5 Hz), 132.97 (quar, J=2.8 Hz), 125.16 (quar, J=3.0 Hz), 122.24 (s), 47.42 (s), 21.80 (s), 8.73 (s). Appendices 5, 6a and 6b.

4.1.5 Triethylammonium tetra(2,4-difluorophenyl)borate (47e)

0.973 g (40 mmol, 1.0 eq) of Mg turnings, 1.09 g (9.96 mmol, 1.0 eq) of sodium tetrafluoroborate, an iodine crystal and 3 ml of THF (freshly distilled, blue color) were added to a flask. 4.5 ml (40 mmol, 1.0 eq) of 1-bromo-2,4-difluorobenzene was dissolved to 26 ml of THF in a dropping funnel. The flask was lowered to a 90 ºC oil bath, 1-bromo-2,4-difluorobenzene solution was added until boiling began, and the oil bath was removed. Rest of the solution was added dropwise, and the mixture was left to stir for 23 h. The mixture was quenched to 40 ml of 4:1:200 Na_2CO_3/NaOH/water solution while stirring. The THF layer was removed. The water layer was saturated with NaCl and extracted with 4 x 30 ml of ether. The ether and THF were combined and washed with 50 ml of brine. The organic layer was evaporated the resulting orange

sludge was dissolved to 300 ml of MeOH/water solution. The solution was filtered through celite to get a clear solution. The liquid did not come through as clear so an additional 60 ml of MeOH was added, and the solution was filtered again through celite. The liquid was now clear. A solution of triethylamine/water/MeOH (3.6/23/3.6 ml) was added slowly. The solution was stirred overnight and placed in freezer. The precipitate was filtered and washed with water + hexane. Creamy solid (2.64 g, 46 % yield); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 7.17 - 7.27 (m, 4H), 6.57 - 6.63 (m, 4H), 6.38 - 6.45 (m, 4H), 3.44 (quar, J=6 Hz, 6H), 1.39 (t, J=7.5 Hz, 9H); C NMR (75 MHz, acetone-d_6) δ (ppm): 166.12 (dd, J=240.8, 10.5 Hz), 160.93 (dd, J=237.0, 12.8 Hz), 137.66 - 137.98 (m), 108.20 (dquar, J=15.0, 3.3 Hz), 101.31 (dquar, J=22.9, 1.6 Hz), 100.89 (dquar, J=23.3, 1.5 Hz), 47.38 (s), 8.71 (s). Appendices 7, 8a and 8b.

4.2 Boroxazolidone preparation

Unpublished research from Kuuloja [3] was used as the basis for preparing these boroxazolidones from the corresponding TEATABs.

4.2.1 4-isopropyl-2,2-diphenyl-1,3λ^4,2λ^4-oxazaborolidin-5-one (25)

1.283 g (11.0 mmol, 1.0 eq) of (L)-valine and 230 ml of toluene were mixed with 4.615 g (11.0 mmol, 1.0 eq) of non-substituted TEATAB **47a**. The solution was refluxed at 120 ºC for 18 h and stirred at room temperature for 4 h. The solid was filtered and washed with 10 ml of water and 10 ml of toluene. White solid (2.94 g, 95% yield); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 7.46 - 7.50 (m, 4H), 7.12 - 7.24 (m, 6H), 6.74 (br. s., 1H), 5.67 (br. s., 1H), 3.68 - 3.75 (m, 1H), 2.31 - 2.42 (m, 1H), 1.12 (d, J=9 Hz, 3H), 1.03 (d, J=6 Hz, 3H). Appendix 9. The spectrum corresponds to Mannoja's spectrum.

4.2.2 4-isopropyl-2,2-bis(4-methylphenyl)-1,3λ^4,2λ^4-oxazaborolidin-5-one (49a)

0.323 g (2.72 mmol, 1.0 eq) of (L)-valine and 1.30 g (2.72 mmol, 1.0 eq) of 4-methyl substituted TEATAB **47c** were mixed with 65 ml of toluene. The solution was refluxed for 19 h at 120 ºC. No solid could be seen, so the solution was evaporated, and the solid was recrystallized with toluene. The solution was placed in a fridge. Solid formed, and it was filtered. The solution was evaporated again, and even less toluene was used to recrystallize again. After 2 days in a freezer, more solid could be filtered out from the solution. The solids were washed with water and toluene. After checking ^{1}H NMR, the fractions were combined. White solid (0.66 g, 78 % yield); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 7.33 - 7.37 (m, 4H), 7.01 - 7.05 (m, 4H), 6.61 (br. s., 1H), 5.53 (br. s., 1H), 3.66 - 3.73 (m, 1H), 2.32 - 2.40 (m, 1H), 2.25 (s, 6H), 1.12 (d, J=6 Hz, 3H),

1.03 (d, J=6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 174.11 (s), 135.31 (s), 135.24 (s), 132.03 (s), 131.97 (s), 128.32 (s), 128.25 (s), 61.01 (s), 29.11 (s), 21.57 (s), 21.53 (s), 19.43 (s), 18.93 (s). Appendices 10, 11a and 11b.

4.2.3 4-isopropyl-2,2-bis(3-methylphenyl)-1,3λ⁴,2λ⁴-oxazaborolidin-5-one (49b)

0.320 g (2.72 mmol, 1.0 eq) of (L)-valine and 1.30 g (2.72 mmol, 1.0 eq) of 3-methyl substituted TEATAB **47d** were mixed with 65 ml of toluene. The solution was refluxed for 18 h at 120 ºC. Solid precipitated after the solution had cooled down for 3 h at room temperature. The solid was filtered and washed with water and toluene. White solid (0.71 g, 85 % yield); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 7.26 - 7.30 (m, 4H), 7.09 (t, J=7.5 Hz, 2H). 6.94 - 6.97 (m, 2H), 3.66 - 3.73 (m, 1H), 2.30 - 2.41 (m, 1H); 2.25 (s, 6H), 1.12 (d, J=6 Hz, 3H), 1.02 (d, J=9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 174.06 (s), 136.10 (s), 135.98 (s), 132.53 (s), 132.49 (s), 128.95 (s), 128.93 (s), 127.61 (s), 127.54 (s), 127.25 (s), 127.19 (s), 61.01 (s), 29.10 (s), 22.10 (s), 19.46 (s), 19.03 (s). Appendices 12, 13a and 13b.

4.2.4 4-isopropyl-2,2-bis(4-methoxyphenyl)-1,3λ⁴,2λ⁴-oxazaborolidin-5-one (49c)

0.26 g (2.4 mmol, 1.0 eq) of (L)-valine, 1.17 g (2.2 mmol, 0.9 eq) of 4-methoxy substituted TEATAB **47b** and 65 ml of toluene were refluxed at 120 ºC for 23 h. Some solid precipitated but it was not enough. The solution was evaporated, and the solid was recrystallized from toluene. Some solid remained undissolved, and the solution was filtered as boiling hot. Evaporated and recrystallized again. After 3 h in a freezer, a solid formed, and it was washed with water and toluene. White solid (0.35 g, 47 % yield); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 7.34 - 7.39 (m, 4H), 6.77 - 6.82 (m, 4H), 3.74 (s, 6H), 3.67 - 3.73 (m, 1H), 2.31 - 2.40 (m, 1H), 1.12 (d, J=6 Hz, 3H), 1.03 (d, J=6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 174.16 (s), 158.61 (s), 158.60 (s), 133.24 (s), 133.13 (s), 113.32 (s), 113.24 (s), 60.99 (s), 55.38 (s), 29.10 (s), 19.44 (s), 18.84 (s). Appendices 14 and 15.

4.2.5 4-isopropyl-2,2-bis(2,4-difluorophenyl)-1,3λ⁴,2λ⁴-oxazaborolidin-5-one (49d)

0.28 g (2.3 mmol, 1.0 eq) of (L)-valine, 1.31 g (2.3 mmol, 0.9 eq) of 2,4-difluoro-substitituted TEATAB **47e** and 65 ml of toluene were refluxed at 130 ºC for 18 h. Recrystallization in toluene did not work. The product had to be purified by column chromatography. The reaction mixture was mixed with silica and dried. 20 cm silica was used, and the starting eluent was 1:3 AcOEt/hexane. White/brown oil, later solid white power (603 mg, 73 % yield); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 7.23 -

7.32 (m, 2H), 6.78 - 6.99 (m, 4H), 5.93 (br. s., 1H), 3.85 - 3.92 (m, 1H), 2.37 - 2.46 (m, 1H), 1.12 (d, J=6 Hz, 3H), 1.08 (d, J=6 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm): 172.27 (s), 166.21 (dd, J=196.1, 11.6 Hz), 166.18 (dd, J=195.0, 12.0 Hz), 162.99 (dd, J=200.6, 11.6 Hz), 162.95 (dd, J=199.1, 12.4 Hz), 135.60 - 136.01 (m), 110.78 (t, J=3.8 Hz), 110.53 (t, J=3.4 Hz), 102.68 (dd, J=29.6, 24.4 Hz), 102.65 (dd, J=29.3, 24.8 Hz), 60.77 (s), 60.75 (s), 18.19 (s), 17.26 (s), 17.23(s). Appendices 16, 17a and 17b.

4.3 Imine condensation

All imine condensation reactions were performed under Ar. The oil bath temperature varied between 80 and 90 ºC. To be able to clearly see refluxing in the flask, a temperature of 85 ºC seemed necessary. Sometimes, the flask lost too much or all of its solvent. To stop the solvent from exiting the system, the following procedures should be used: Removing the Ar balloon after flushing the system, sealing the system with additional Teflon-tape, not lowering the flask deeper into the oil than is necessary and using only septa that are still in good condition.

TLC was done to determine the formation of product(s). All products were purified by column chromatography. The sample for the column was prepared by mixing the reaction mixture with silica gel and evaporating the solvent. Between 22 and 30 cm of silica gel was used for the column. Starting eluent ranged from 1:4 to 1:12 AcOEt/hexane. More silica and less polar eluent are generally needed for aldehydes other than benzaldehyde. The aldehyde came out first and then the product. Eluent polarity was increased after some time to get the product out faster but not too much as not to push out the boroxazolidone. Product fractions were combined and evaporated.

4.3.1 3-benzyl-4-isopropyl-2,2-diphenyl-1,3λ^4,2λ^4-oxazaborol-5-one (65a)

140 mg (0.5 mmol, 1.0 eq) of boroxazolidone **25**, 2 ml of DCE, 0.25 ml (2.5 mmol, 5.0 eq) of benzaldehyde and 0.15 mmol, (0.3 eq) of Lewis base were mixed in this order and kept in a 80 ºC oil bath for 24 h. White/creamy solid (105 mg, 57 % yield, TBD as LB); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.42 - 7.48 (m, 4H), 7.30 - 7.37 (m, 6H), 7.08 - 7.21 (m, 3H), 6.49 (d, J=9 Hz, 2H), 5.00 (s, 2H), 2.99 (quin, J= 6 Hz, 1H), 1.25 (d, J=9 Hz, 6H). Appendix 18. This spectrum corresponds to Mannoja's spectrum.

4.3.2 3-benzylidene-4-isopropyl-2,2-diphenyl-1,3λ^4,2λ^4-oxazaborolidin-5-one (65b)

This was done similarly to ketimine **65a**. 8.1 mg (0.15 mmol, 0.3 eq) of sodium methoxide was used as the LB. Even when the product seemed pure on TLC after running column, ^{1}H NMR showed a mixture of aldimine **65b**, boroxazolidone **25** and benzaldehyde. I.e. the product reverted to its starting materials. White solid (89 mg, 48

%, not pure); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.88 (d, J=3 Hz, 1H), 7.70 - 7.85 (m, 3H), 7.59 - 7.62 (m, 2H), 7.23 - 7.40 (m, 7H), 5.36 (t, J=3 Hz, 1H), 2.12 - 2.25 (m, 1H), 1.20 (d, J=9 Hz, 3H), 0.66 (d, J=6 Hz, 3H). Appendix 19. This spectrum does not entirely match Mannoja's spectrum of this compound.

4.3.3 3-(4-methoxybenzyl)-4-isopropyl-2,2-diphenyl-1,3λ⁴,2λ⁴-oxazaborol-5-one (67a)

139 mg (0.5 mmol, 1.0 eq) of boroxazolidone **25**, 2 ml of DCE, 0.28 ml (2.5 mmol, 5.0 eq) of 4-methoxybenzaldehyde and 21.0 mg (0.15 mmol, 0.3 eq) of TBD were mixed and kept in a 90 ºC oil bath for 24 h. Yellow solid (81 mg, 40 % yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.42 - 7.47 (m, 4H), 7.31 - 7.35 (m, 6H), 6.61 (d, J=9 Hz, 2H), 6.38 (d, J=9 Hz, 2H), 4.93 (s, 2H), 3.71 (s, 3H), 3.04 (quin, J=7.5 Hz, 1H), 1.24 (d, J=9 Hz 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 175.54 (s), 162.89 (s), 159.63 (s), 134.96 (s), 133.13 (s), 128.87 (s), 128.24 (s), 127.99 (s), 125.89 (s), 114.48 (s), 55.46 (s), 51.65 (s), 30.15 (s), 17.96 (s). Appendices 20 and 21.

4.3.4 3-(4-bromobenzyl)-4-isopropyl-2,2-diphenyl-1,3λ⁴,2λ⁴-oxazaborol-5-one (67b)

142 mg (0.5 mmol, 1.0 eq) of boroxazolidone **25**, 2 ml of DCE, 464 mg (2.5 mmol, 5.0 eq) of 4-bromobenzaldehyde and 21.0 mg (0.15 mmol, 0.3 eq) of TBD were mixed and kept in a 90 ºC oil bath for 24 h. Yellow solid (137 mg, 61 % yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.39 - 7.46 (m, 4H), 7.30 -7.34 (m, 6H), 7.21 - 7.25 (m, 2H), 6.31 (d, J=9 Hz, 2H), 4.94 (s, 2H), 2.95 (quin, J=6 Hz, 1H), 1.28, d, J=6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 176.01 (s), 162.59 (s), 134.96 (s), 133.05 (s), 132.77 (s), 132.33 (s), 128.90 (s), 128.35 (s), 128.16 (s), 122.78 (s), 51.36 (s), 30.24 (s), 18.04 (s). Appendices 22, 23a and 23b.

4.3.5 3-(4-fluorobenzyl)-4-isopropyl-2,2-diphenyl-1,3λ⁴,2λ⁴-oxazaborol-5-one (67c)

140 mg (0.5 mmol, 1.0 eq) of boroxazolidone **25**, 2 ml of DCE, 0.27 ml (2.5 mmol, 5.0 eq) of 4-fluorobenzaldehyde and 21.0 mg (0.15 mmol, 0.3 eq) of TBD were mixed and kept in a 90 ºC oil bath for 24 h. White solid (117 mg, 60 % yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.42 - 7.45 (m, 4H), 7.31 - 7.33 (m, 6H), 6.79 (t, J=9 Hz, 2H), 6.40 - 6.45 (m, 2H), 4.69 (s, 2H), 2.98 (quin, J=6 Hz, 1H), 1.27 (d, J=6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 175.87 (s), 162.67 (s), 162.53 (d, J=247.5 Hz), 134.97 (s), 133.07 (s), 129.64 (d, J=3.75 Hz), 129.24 (d, J=7.5 Hz), 128.30 (s), 128.10 (s), 116.20 (d, J=22.5 Hz), 51.29 (s), 30.21 (s), 17.98 (s). Appendices 24, 25a and 25b.

4.3.6 3-(4-nitrobenzyl)-4-isopropyl-2,2-diphenyl-1,3λ⁴,2λ⁴-oxazaborol-5-one (67e)

142 mg (0.5 mmol, 1.0 eq) of boroxazolidone **25** and 2 ml of DCE were mixed and heated in a 90 ºC oil bath. 377 mg (2.5 mmol, 5.0 eq) of 4-nitrobenzaldehyde was dissolved in 1 ml of DCE and heated in the oil bath. This was done to make sure that both the aldehyde and boroxazolidone are better dissolved before mixing them, in case that this has an effect. The aldehyde/DCE solution and 21.0 mg (0.15 mmol, 0.3 eq) of TBD were added to the flask and were kept in a 90 ºC oil bath for 24 h. Beige solid (45 mg, 42 % yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.91 - 7.96 (m, 2H), 7.39 - 7.42 (m, 4H), 7.28 - 7.33 (m, 6H), 6.60 (d, J=9 Hz, 2H), 5.08 (s, 2H), 2.89 (quin, J=9 Hz, 1H), 1.33 (d, J=6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 176.56 (s), 162.26 (s), 147.76 (s), 140.44 (s), 132.99 (s), 130.73 (s), 128.46 (s), 128.35 (s), 127. 92 (s), 124.23 (s), 51.03 (s), 30.35 (s), 18.15 (s). Appendices 26, 27a and 27b.

4.3.7 3-(4-Trifluoromethylbenzyl)-4-isopropyl-2,2-diphenyl-1,3λ⁴,2λ⁴-oxazaborol-5-one (67f)

142 mg (0.5 mmol, 1.0 eq) of boroxazolidone **25** and 2 ml of DCE were mixed and heated in a 90 ºC oil bath for a few minutes to first dissolve the boroxazolidone. After the flask had cooled a bit, 0.34 ml (2.5 mmol, 5.0 eq) of 4-trifluoromethylbenzaldehyde and 21.0 mg (0.15 mmol, 0.3 eq) of TBD were added. The mixture was kept in a 90 ºC oil bath for 24 h. Yellow solid (142 mg, 63 % yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.39 - 7.45 (m, 4H), 7.37 (s, 1H), 7.30 - 7.34 (m, 7H), 6.57 (d, J=9 Hz, 2H), 5.05 (s, 2H), 2.92 (quin, J=7.5 Hz, 1H), 1.29 (d, J=9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 176.24 (s), 162.55 (s), 137.61 (s), 137.60 (s), 133.04 (s), 130.77 (quar, J=33 Hz), 128.38 (s), 128.22 (s), 127.62 (s), 126.05 (quar, J=3.8 Hz), 123.79 (quar, J=271 Hz), 51.37 (s), 30.25 (s), 18.01 (s). Appendices 28, 29a and 29b.

4.3.8 3-(3-Trifluoromethylbenzyl)-4-isopropyl-2,2-diphenyl-1,3λ⁴,2λ⁴-oxazaborol-5-one (67g)

This was done similarly to **67f**. 142 mg (0.5 mmol, 1.0 eq) of boroxazolidone **25**, 2 ml of DCE, 0.33 ml mg (2.5 mmol, 5.0 eq) of 3-trifluoromethylbenzaldehyde and 21 mg (0.15 mmol, 0.3 eq) of TBD were used. White solid (115 mg, 52 % yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.40 - 7.45 (m, 5H), 7.29 - 7.33 (m, 6H), 7.22 - 7.27 (m, 1H), 6.68 - 6.73 (m, 2H), 5.06 (s, 2H), 2.93 (quin, J=6 Hz, 1H), 1.30 (d, J=6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 176.20 (s), 162.48 (s), 134.62 (s), 132.99 (s), 131.71 (quar, J=33.7 Hz), 130.47 (s), 129.70 (s), 128.38 (s), 128.24 (s), 125.44 (quar, J=3.7 Hz), 123.93 (quar, J=4.0 Hz), 51.31 (s), 30.31 (s), 18.00 (s). Appendices 30, 31a and 31b.

4.3.9 3-(2-Trifluoromethylbenzyl)-4-isopropyl-2,2-diphenyl-1,3λ⁴,2λ⁴-oxazaborol-5-one (67h)

This was done similarly to **67f**. 142 mg (0.5 mmol, 1.0 eq) of boroxazolidone **25**, 2 ml of DCE, 0.33 ml mg (2.5 mmol, 5.0 eq) of 2-trifluoromethylbenzaldehyde and 20.6 mg (0.15 mmol, 0.3 eq) of TBD were used. Yellow solid (18 mg, 8 % yield, 8 mol % aldehyde); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.62 (d, J=9 Hz, 1H), 7.40 - 7.44 (m, 4H), 7.27 - 7.32 (m, 7H), 7.08 (t, J=7.5 Hz, 1H), 5.97 (d, J=9 Hz, 1H), 5.17 (s, 2H), 2.76 (quin, J=6 Hz, 1H), 1.33 (d, J=6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 176.74 (s), 162.35 (s), 132.89 (s), 132.45 (s) 132.44 (s), 131.90 (quar, J=1.5 Hz), 130.74 (s), 128.49 (s), 128.34 (s), 128.13 (s), 127.25 (s), 126.47 (quar, J=6 Hz), 47.89 (s), 47.85 (s), 30.10 (s), 17.95 (s). Appendices 32, 33a and 33b.

4.3.10 3-(4-Cyanobenzyl)-4-isopropyl-2,2-diphenyl-1,3λ⁴,2λ⁴-oxazaborol-5-one (67i)

This was done similarly to **67e**. 141 mg (0.5 mmol, 1.0 eq) of boroxazolidone **25**, 2+1 ml of DCE, 327 mg (2.5 mmol, 5.0 eq) of 4-cyanobenzaldehyde and 21 mg (0.15 mmol, 0.3 eq) of TBD were used. Oil T was 85 ºC. Creamy solid (73 mg, 35 % yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.35 - 7.42 (m, 6H), 7.28 - 7.33 (m, 6H), 6.54 (d, J=9 Hz, 2H), 5.04 (s, 2H), 2.88 (quin, J=6 Hz, 1H), 1.31 (d, J=6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 176.45 (s), 162.31 (s), 138.61 (s), 133.00 (s), 132.80 (s), 130.13 (s), 128.41 (s), 128.29 (s), 127.72 (s), 118.03 (s), 112.65 (s), 51.27 (s), 30.31 (s), 18.13 (s). Appendices 34 and 35.

4.3.11 3-(4-Methyl carboxylatebenzyl)-4-isopropyl-2,2-diphenyl-1,3λ⁴,2λ⁴-oxazaborol-5-one (67l)

This was done similarly to **67e**. 139 mg (0.5 mmol, 1.0 eq) of boroxazolidone **25**, 2+1 ml of DCE, 410 mg (2.5 mmol, 5.0 eq) of methyl benzaldehyde-4-carboxylate and 22 mg (0.15 mmol, 0.3 eq) of TBD were used. Oil T was 85 ºC. White solid (95 mg, 43 % yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.76 (d, J=9 Hz, 2H), 7.42 - 7.47 (m, 4H), 7.30 - 7.32 (m, 6H), 6.53 (d, J=9 Hz, 2H), 5.04 (s, 2H), 3.87 (s, 3H), 2.92 (quin, J=6 Hz, 1H), 1.28 (d, J=6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 176.17 (s), 166.35 (s), 162.53 (s), 138.52 (s), 134.94 (s), 133.03 (s), 130.40 (s), 130.34 (s), 128.32 (s), 128.16 (s), 127.14 (s), 52.48 (s), 51.62 (s), 30.26 (s), 18.01 (s). Appendices 36, 37a and 37b.

4.3.12 3-(Benzyl)-4-isopropyl-2,2-bis(4-methylphenyl)-1,3λ⁴,2λ⁴-oxazaborol-5-one (68a)

This was done similarly to **67f**. 154 mg (0.5 mmol, 1.0 eq) of 4-methyl-substituted boroxazolidone **49a**, 2 ml of DCE, 0.25 ml mg (2.5 mmol, 5.0 eq) of benzaldehyde and

21 mg (0.15 mmol, 0.3 eq) of TBD were used. Creamy solid (97 mg, 48 % yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.34 (d, J=6 Hz, 4H), 7.12 - 7.16 (m, 7H), 6.52 (d, J=6 Hz, 2H), 4.98 (s, 2H), 2.97 (quin, J=6 Hz, 1H), 2.35 (s, 6H), 1.24 (d, J=6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 175.44 (s), 162.86 (s), 137.49 (s), 135.08 (s), 134.03 (s), 133.13 (s), 129.15 (s), 128.99 (s), 128.51 (s), 127.39 (s), 52.05 (s), 30.16 (s), 21.51 (s), 17.90 (s). Appendices 38, 39a and 39b.

4.3.13 3-(Benzyl)-4-isopropyl-2,2-bis(3-methylphenyl)-1,3λ⁴,2λ⁴-oxazaborol-5-one (68b)

This was done similarly to **67f**. 157 mg (0.5 mmol, 1.0 eq) of 3-methyl-substituted boroxazolidone **49b**, 2 ml of DCE, 0.25 ml mg (2.5 mmol, 5.0 eq) of benzaldehyde and 21 mg (0.15 mmol, 0.3 eq) of TBD were used. The temperature was 85 ºC. Creamy solid (120 mg, 60 % yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.10 - 7.27 (m, 11H), 6.53 (d, J=6 Hz, 2H), 5.01 (s, 2H), 3.01 (quin, J=6 Hz, 1H), 3.32 (s, 6H), 1.26 (d, J=9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 175.57 (s), 162.86 (s), 137.46 (s), 133.91 (s), 130.02 (s), 129.22 (s), 129.15 (s), 128.71 (s), 128.55 (s), 128.09 (s), 127.39 (s), 52.12 (s), 30.17 (s), 21.91 (s), 12.97 (s). Appendices 40, 41a and 41b.

4.3.14 3-(Benzyl)-4-isopropyl-2,2-bis(4-methoxyphenyl)-1,3λ⁴,2λ⁴-oxazaborol-5-one (68c)

This was done similarly to **67f**. 171 mg (0.5 mmol, 1.0 eq) of 4-methoxy-substituted boroxazolidone **49c**, 2 ml of DCE, 0.25 ml (2.5 mmol, 5.0 eq) of benzaldehyde and 21.5 mg (0.15 mmol, 0.3 eq) of TBD were used. The temperature was 85 ºC. Creamy solid (62 mg, 29 % yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.33 - 7.38 (m, 4H), 7.10 - 7.19 (m, 3H), 6.85 - 6.90 (m, 4H), 6.54 (d, J=6 Hz, 2H), 4.95 (s, 2H), 3.81 (s, 6H), 2.97 (quin, J=6 Hz, 1H), 1.24 (d, J=9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 175.27 (s), 162.82 (s), 159.67 (s), 136.85 (s), 134.37 (s), 133.98 (s), 129.20 (s), 128.54 (s), 127.32 (s), 113.83 (s), 55.32 (s), 51.94 (s), 31.14 (s), 17.93 (s). Appendices 42, 43a and 43b.

4.3.15 3-(Benzyl)-4-isopropyl-2,2-bis(2,4-difluorophenyl)-1,3λ⁴,2λ⁴-oxazaborol-5-one (68d)

175 mg (0.5 mmol, 1.0 eq) of boroxazolidone **49d**, 2 ml of DCE, 0.25 ml (2.5 mmol, 5.0 eq) of benzaldehyde and 21.0 mg (0.15 mmol, 0.3 eq) of TBD were mixed and kept in 85 ºC oil bath for 24 h. Creamy solid (115 mg, 52 % yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.36 - 7.46 (m, 2H), 7.12 - 7.24 (m, 3H), 6.82 - 6.88 (m, 2H), 6.57 - 6.68 (m, 4H), 5.15 (s, 2H), 3.02 (quin, J=6 Hz, 1H), 1.32 (d, J=9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.22 (s), 166.55 (dd, J=168.0, 12.8 Hz), 163.30 (dd=174.4, 12.4 Hz), 162.20 (s), 136.96 - 137.24 (m), 133.57 (s), 129.15 (s), 128.40 (s), 126.35 (s),

111.65 (dd, J=19.1, 3.4 Hz), 103.40 (dd, J=30.0, 24.0 Hz), 51.94 - 52.08 (m), 30.00 (s), 17.54 (s). Appendices 44, 45a, 45b and 45c.

4.4 Additional procedures

4.4.1 Preparation of 4-bromobenzotriflate (70)

The dichloromethane (DCM) used in this reaction was dried by distilling it over sodium. 9.45 g (54.7 mmol, 1.0 eq) of 4-bromophenol **69** was mixed with 54 ml of dry DCM. 13.5 ml (54.7 mmol, 1.5 eq) of trifluoromethane sulfonic anhydride was mixed with 54 ml of dry DCM. 4.5 ml (54.7 mmol, 1.0 eq) of pyridine was added to the bromophenol solution while stirring and the mixture was put in a -70 ºC liquid nitrogen / acetone bath. Trifluoromethane sulfonic anhydride solution was slowly added while stirring. Solution was allowed to warm to room temperature and stirred for 24 h. 100 ml of water and DCM were added. The DCM was separated and washed with 3 x 100 ml of water and 100 ml of brine. Dried with sodium sulfate and evaporated. The mixture was flushed twice through a column containing 5 cm of silica by using only DCM as the eluent to remove impurities. Magnesium sulfate was used to further remove moisture. Yellow liquid (15.09 g, 90 % yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.54 - 7.63 (m, 2H), 7.14 - 7.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 148.69 (s), 133.62 (s), 123.27 (s), 122.25 (s), 118.91 (quar, J=319 Hz). Appendices 46 and 47.

4.4.2 Preparation of methyl benzaldehyde-4-carboxylate (72)

506 mg (3.66, 1.1 eq) of potassium carbonate was mixed with 12 ml of MeOH. 500 mg (3.33 mmol, 1.0 eq) of 4-carboxybenzladehyde **71** and 0.95 ml (9.99 mmol, 3.0 eq) dimethyl sulfate were added to the solution while stirring. The solution was stirred at room temperature for 3 h. The solution was evaporated; 15 ml of water was added, extracted with 3 x 10 ml of ether and dried with sodium sulfate. The mixture was purified with column chromatography. 1:4 AcOEt/hexane eluent was used. Beige solid (413 mg, 75 % yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 10.10 (s, 1H), 8.18 - 8.21 (m, 2H), 7.93 - 7.97 (m, 2H), 3.96 (s, 3H). Appendix 48. ^{1}H NMR spectrum matches to the one of the same compound on Sigma-Aldrich's website [58].

5. CONCLUSIONS

Five different TEATABs were successfully prepared with yields ranging from 13 to 95 %. The TEATABs were substituted with hydrogen, 4-methoxy, 4-methyl, 3-methyl and 2,4-difluoro groups. The best yield of 95 % was achieved with the non-substituted TEATAB, but it was made from commercial sodium tetraphenylborate, and the others were made via Grignard reactions by using different aryl bromides. The yield from this reaction depends highly on the solubility difference of the NaTAB and TEATAB in a water/methanol solvent system. Attempts to produce 4-nitrile and 4-triflate-substituted TEATABs were unsuccessful. The Grignard reaction for 4-bromobenzonitrile failed, and the 4-triflate-substituted TEATAB reaction seemed to produce a mixture of triarylborate and tetra-arylborate.

Five different boroxazolidones were successfully prepared from the TEATABs and (L)-valine with yields varying from 95 to 47 %. The best yield was achieved with the non-substituted TEATAB and the lowest with 4-methoxy-substituted TEATAB. The yield from this reaction is highly dependent on the low solubility of the boroxazolidone to the reaction solvent. The 2,4-difluoro-substituted boroxazolidone had to be purified by column chromatography because of its high solubility to the reaction solvent, after which a good yield was achieved.

The imine condensation reaction of non-substituted boroxazolidone and benzaldehyde, already improved by Mannoja, was further studied with different Lewis bases. The yield of 62 % for the ketimine reported in her thesis could not be replicated with any Lewis base. The best yield of this ketimine achieved in this study was 57 % with TBD as the LB. It was found that NaOMe works better for producing the aldimine than the triphenylphosphate PPh_3 reported by Mannoja. PPh_3 is reported to produce a conversion of 13 % of aldimine whereas with NaOMe, a 48 % yield was achieved. However, this yield is an estimate because the purity could not be confirmed by ^1H NMR. This was because the aldimine quickly degraded back to the boroxazolidone and benzaldehyde.

Mannoja suggested that the formation of either the ketimine or aldimine would depend on the catalyzing base either being only a Lewis base in the case of aldimine or being a Lewis and Brønsted base in the case of ketimine. The two different pathways presented in Scheme 12 for Lewis bases and Brønsted bases to produce an imine would explain the route to a ketimine or an aldimine. However, NaOMe and TBD are both Lewis and Brønsted bases so the reason behind either a ketimine or an aldimine forming must be something else.

Different aldehydes were tested for producing the ketimine from non-substituted boroxazolidone. The best yields were achieved with halogen-substituted benzaldehydes with 4-bromo, 4-fluoro and 4-(trifluoromethyl)benzaldehydes having almost equal yields of 61, 60 and 63 %, respectively. The yields become lower when using benzaldehydes with non-halogenated electron withdrawing substituents, and with the exception of 4-methoxybenzaldehyde, no product is formed at all with aldehydes containing electron donating substituents. This makes sense when one thinks that electron withdrawing substituents make the carbonyl more electrophilic and thus the imine formation becomes easier. However, this does not explain why halogen-substituents have a bigger effect on the yield than electron withdrawing non-halogen substituents or why non-substituted benzaldehyde produces a better yield than many benzaldehydes with electron withdrawing substituents.

Finally, the four remaining boroxazolidones were tested with benzaldehyde. Yields ranged from 60 to 29 % with 3-methyl-substituted boroxazolidone producing the highest yield and 4-methoxy-substituted boroxazolidone producing the lowest yield. It was hoped that these tests could show if changing the boron's substituents would affect the N-B bond and thus the nitrogen's nucleophilicity and finally imine formation yield. However, there seems to be no clear correlation between electron donating substituents on the boron and a higher yield or vice versa. The following order of procedures was found to be the best for the imine reactions: adding the boroxazolidone and solvent, preheating, cooling, adding the aldehyde, adding the LB and finally setting the mixture to barely reflux at 85 °C. Formation of multiple products should always be avoided. This is affected by the choice of the LB, temperature, the aldehyde and the boroxazolidone.

This investigation produced two clear results. First, the formation of either a ketimine or an aldimine does not depend on the catalyst base being only a Lewis base or also a Brønsted base because both TBD and NaOMe belong to these two categories. Secondly, the imine yield usually increases as the benzaldehyde's substituents become more electron withdrawing. It is difficult to make any other conclusions from this data. More boroxazolidones with differing substituents at the boron should be tested to see if a correlation between the boron's substituents and the imine yield could be found. Crystallographic measurements would give direct information about the boroxazolidones' and imines' N-B bonds' strength. It would be interesting to see how the substituents affect the bond strength and how this correlates with the imine yields. One practical area of improvement regarding these imines would be the column chromatography. The compounds are not very soluble in AcOEt/hexane, which leads to using a large amount of solvent for every purification, about 500 - 800 ml. A chloroform/hexane eluent system might be more efficient but it was not tested. An inherent problem of the reaction chain from an aryl bromide to a TEATAB, to a boroxazolidone and finally to the imine, is the low atom economy.

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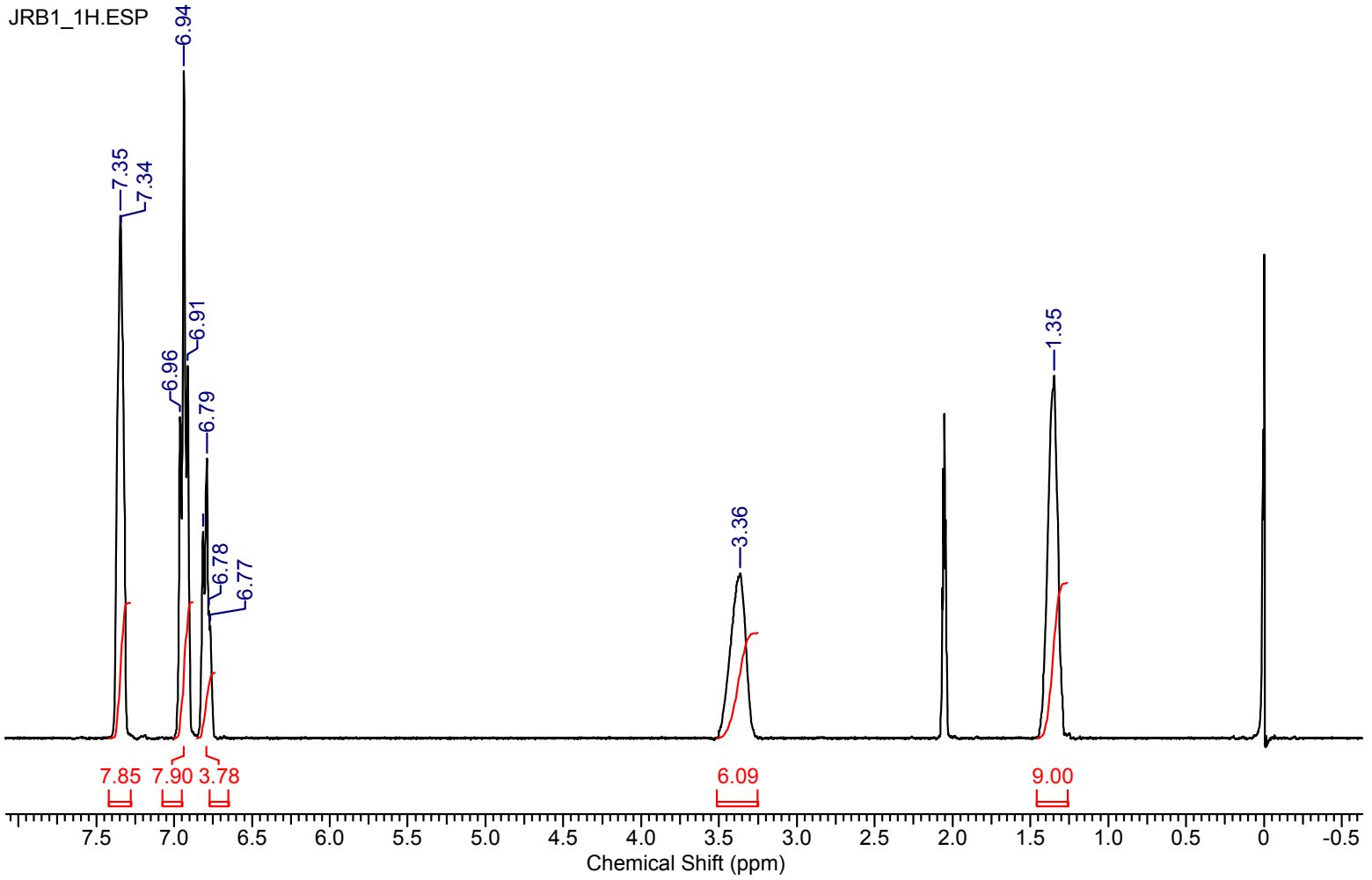
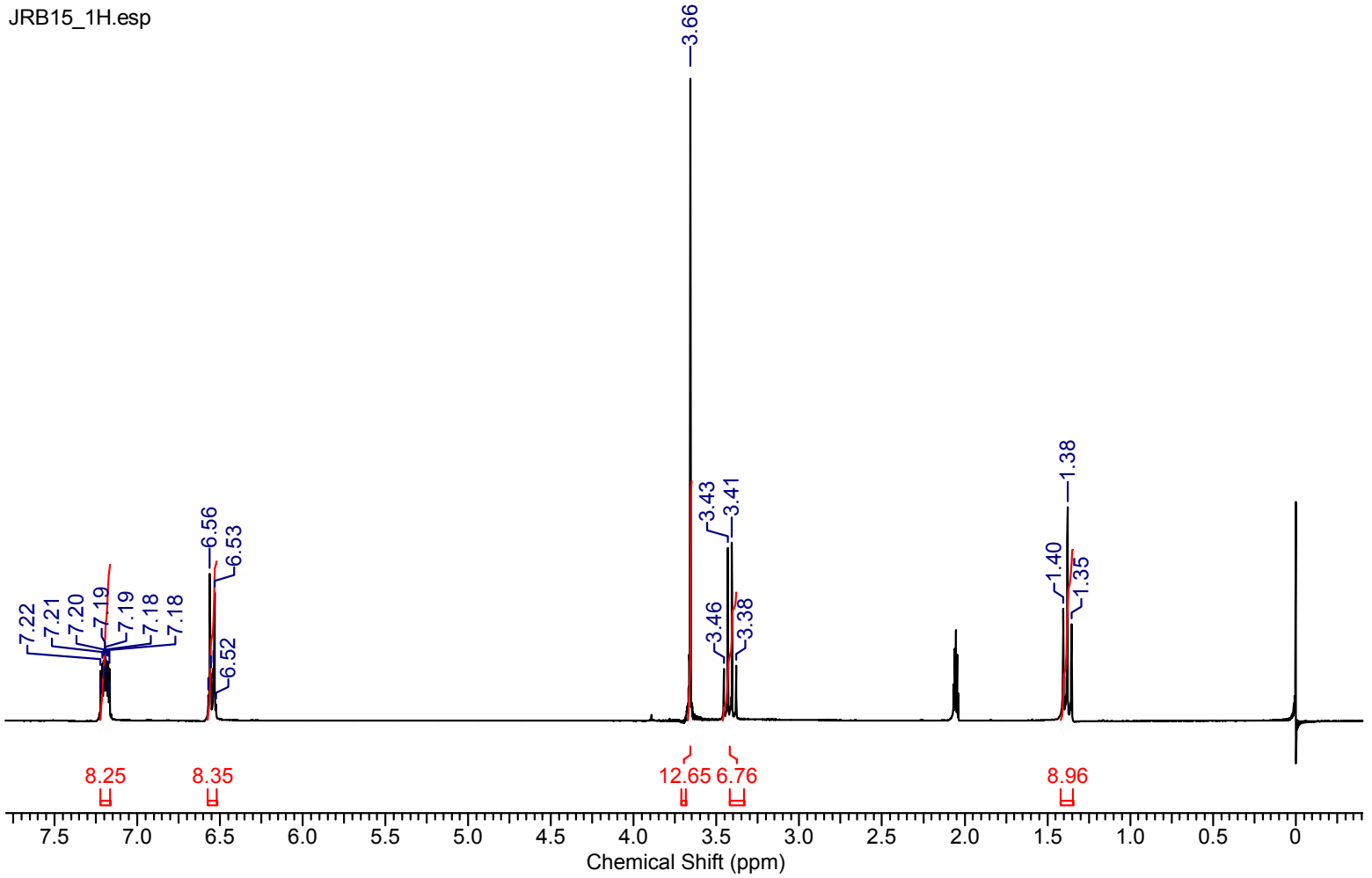
APPENDICES

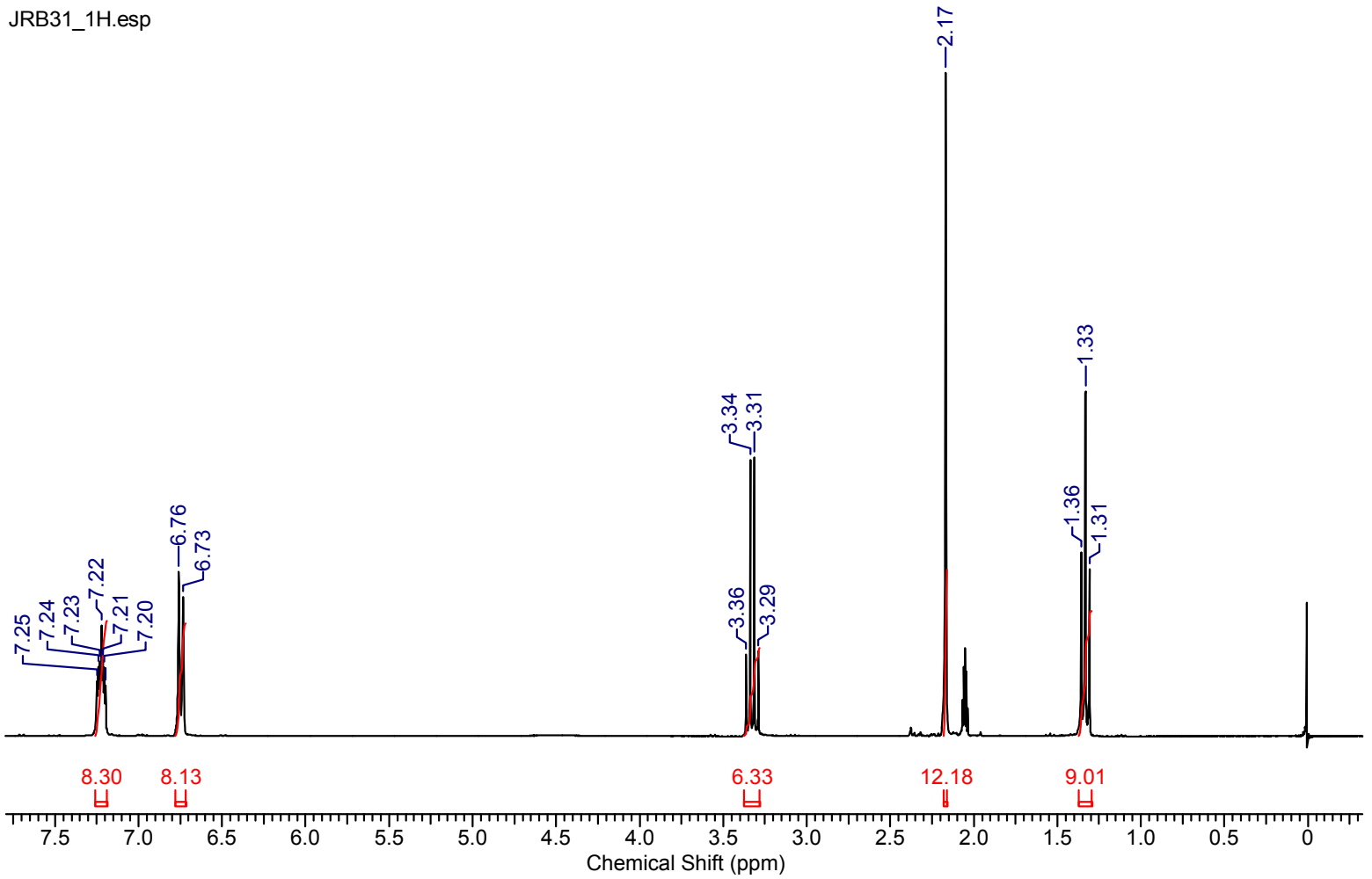
APPENDIX 1: ^{1}H NMR FOR COMPOUND 47A



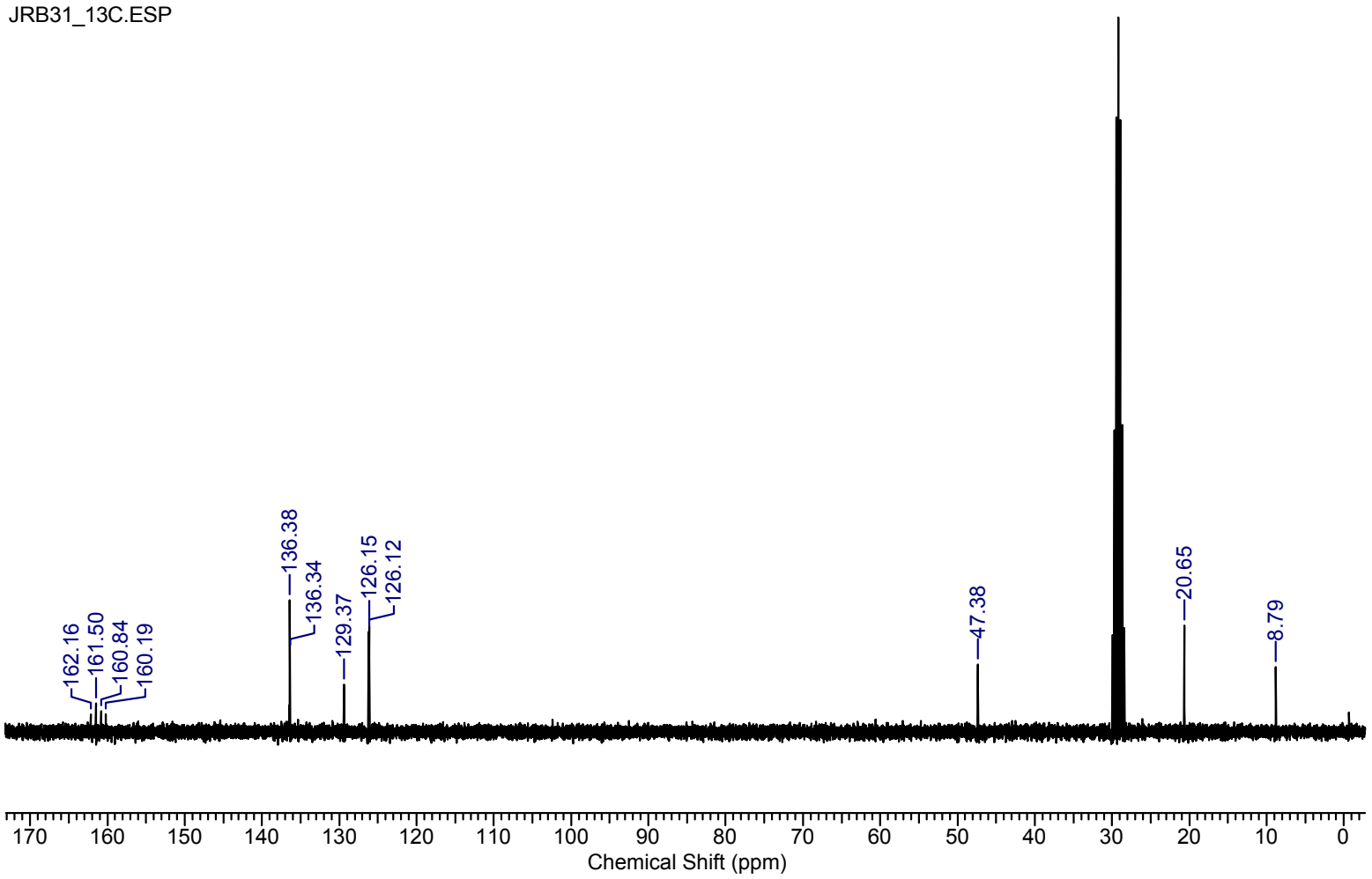
APPENDIX 2: ^{1}H NMR FOR COMPOUND 47B



APPENDIX 3: ^{1}H NMR FOR COMPOUND 47C

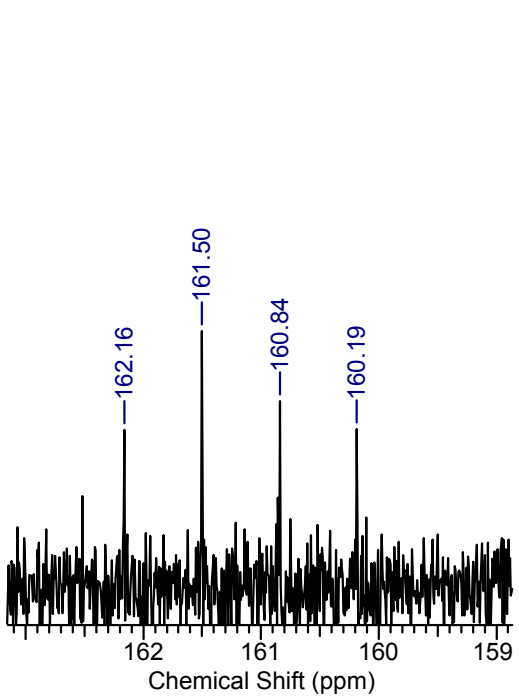


APPENDIX 4A: ^{13}C NMR FOR COMPOUND 47C

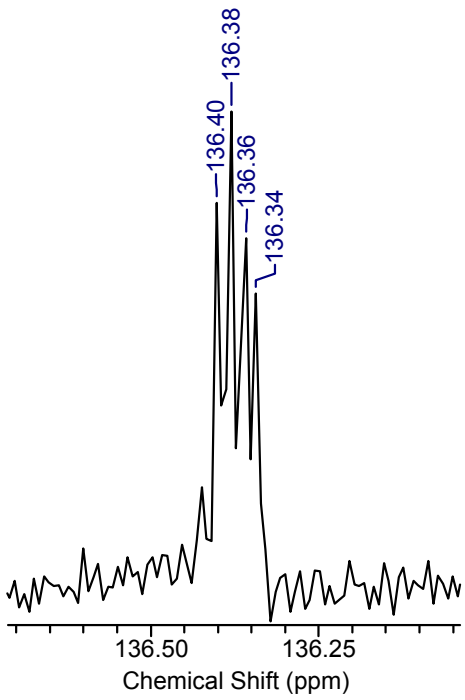


APPENDIX 4B: ^{13}C NMR CLOSE-UPS FOR COMPOUND 47C

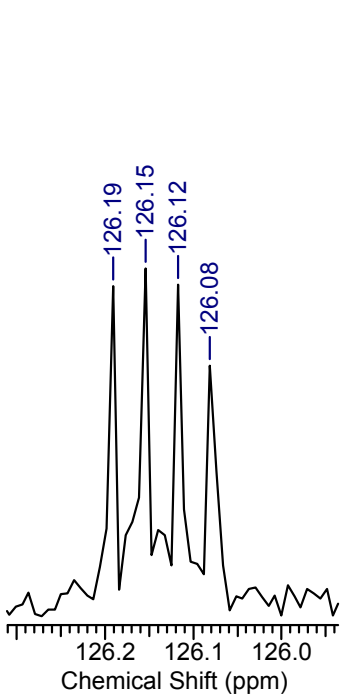
JRB31_13C.esp



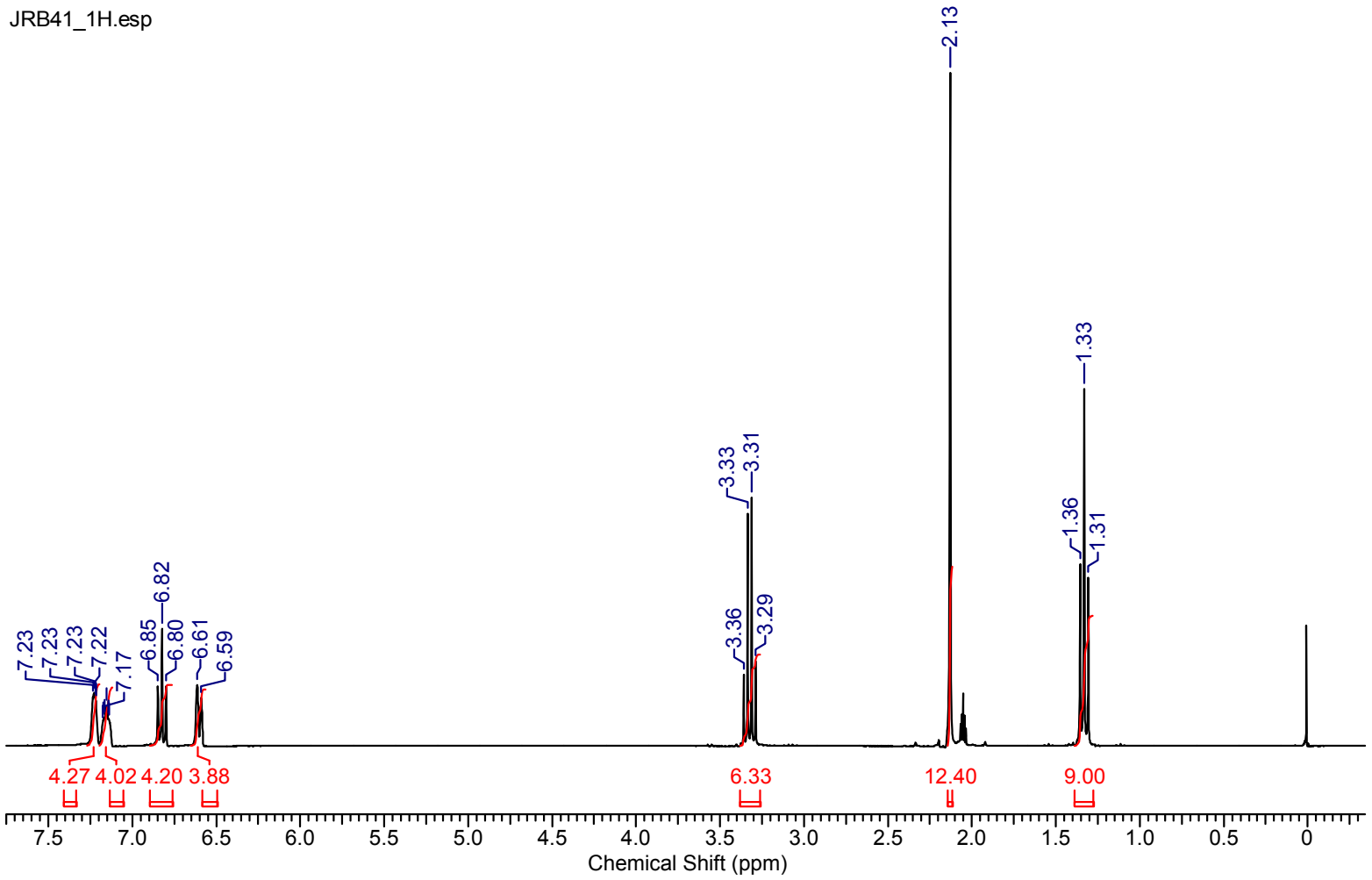
JRB31_13C.esp



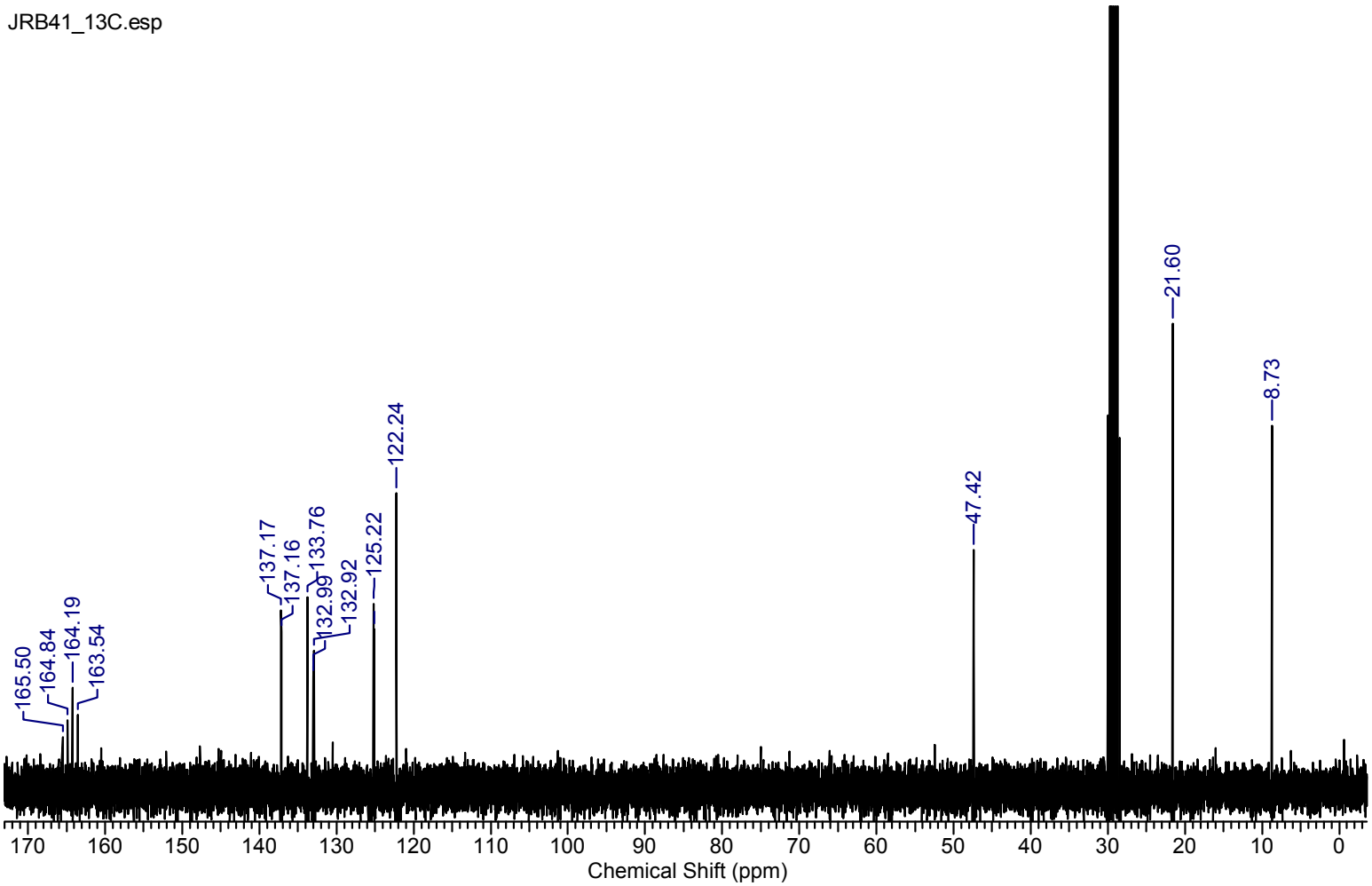
JRB31_13C.esp



APPENDIX 5: ^{1}H NMR FOR COMPOUND 47D

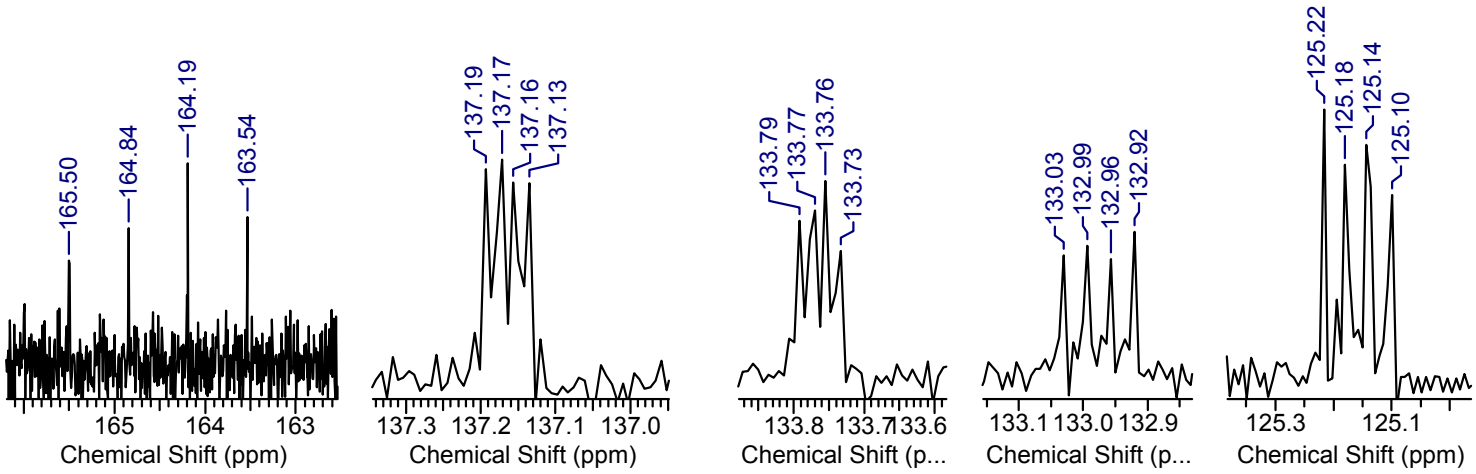


APPENDIX 6A: ^{13}C NMR FOR COMPOUND 47D

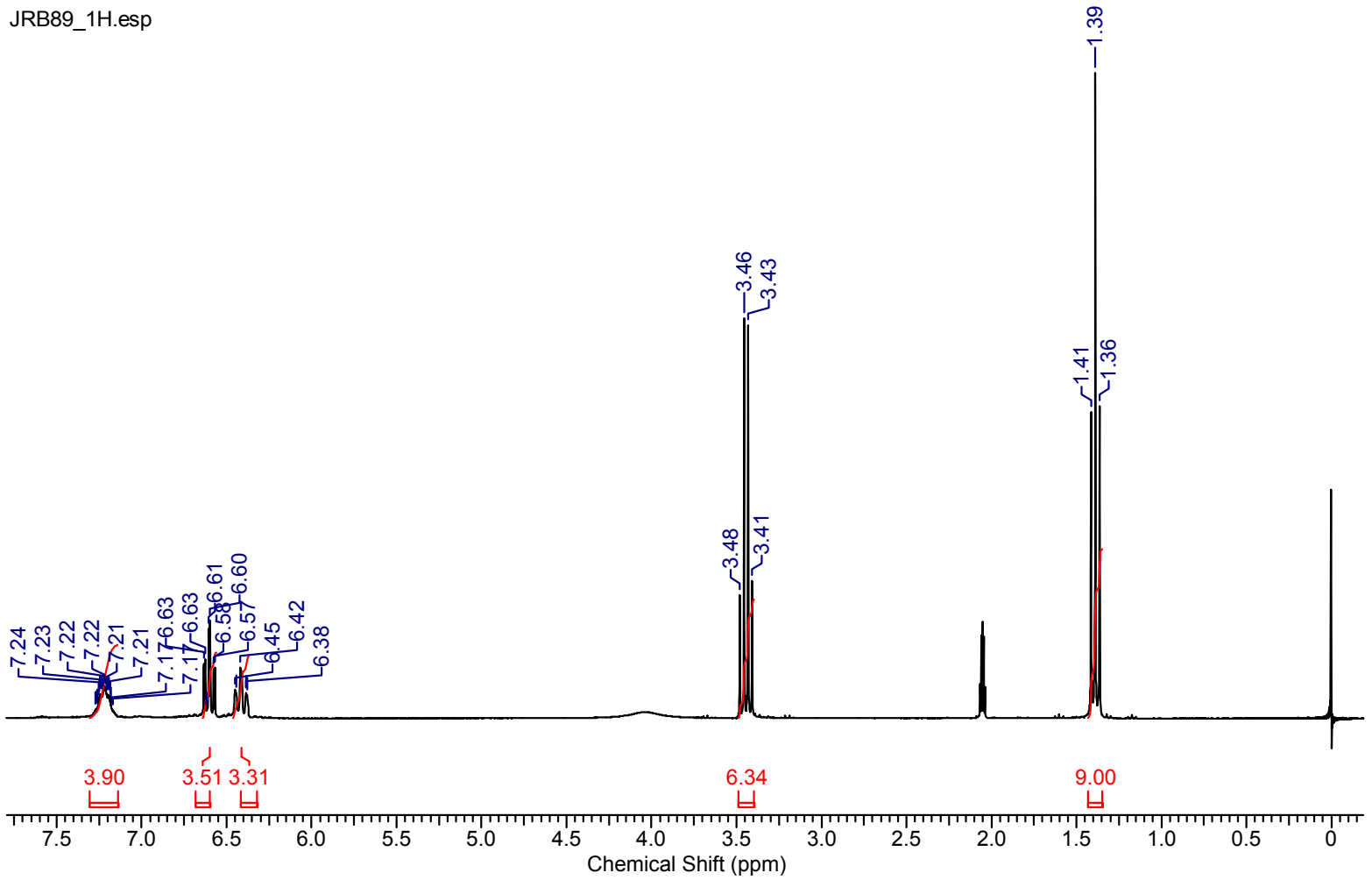


APPENDIX 6B: ^{13}C NMR CLOSE-UPS FOR COMPOUND 47D

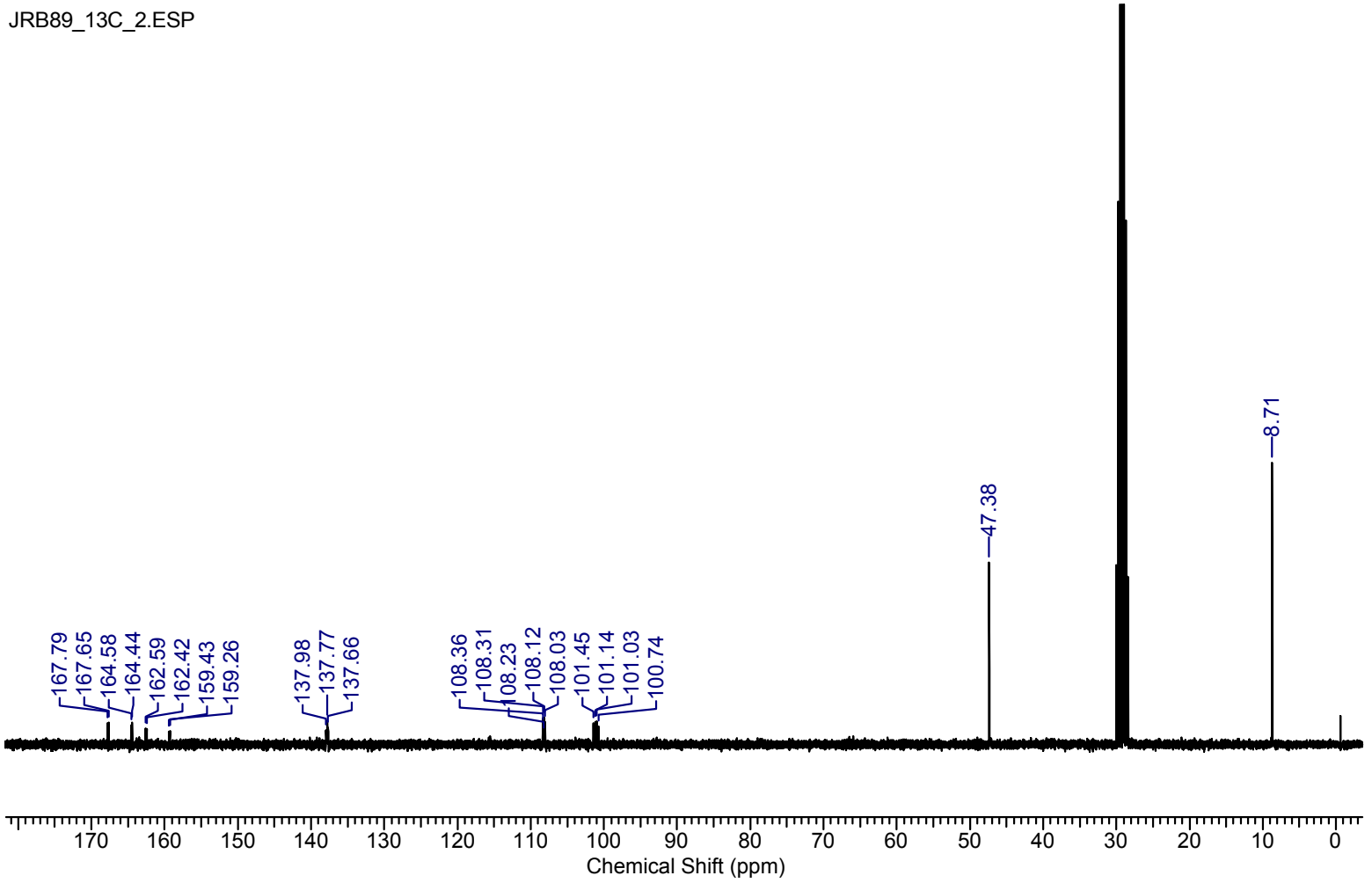
JRB41_13C.esp JRB41_13C.esp JRB41_13C.esp JRB41_13C.esp JRB41_13C.esp



APPENDIX 7: ^{1}H NMR FOR COMPOUND 47E



APPENDIX 8A: ^{13}C NMR FOR COMPOUND 47E



APPENDIX 8B: ^{13}C NMR CLOSE-UPS FOR COMPOUND 47E

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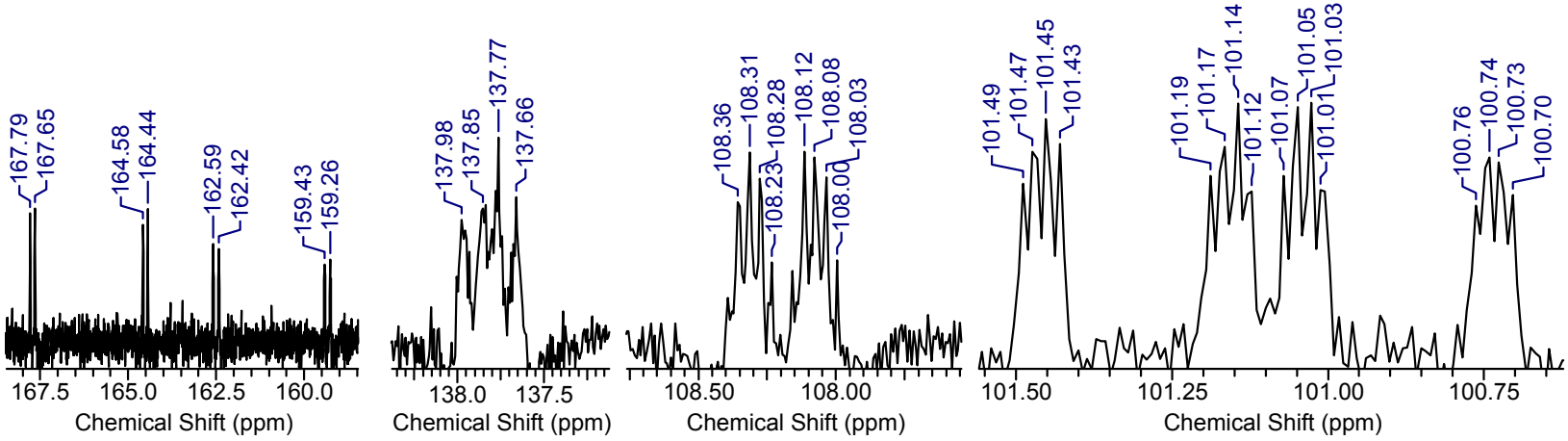
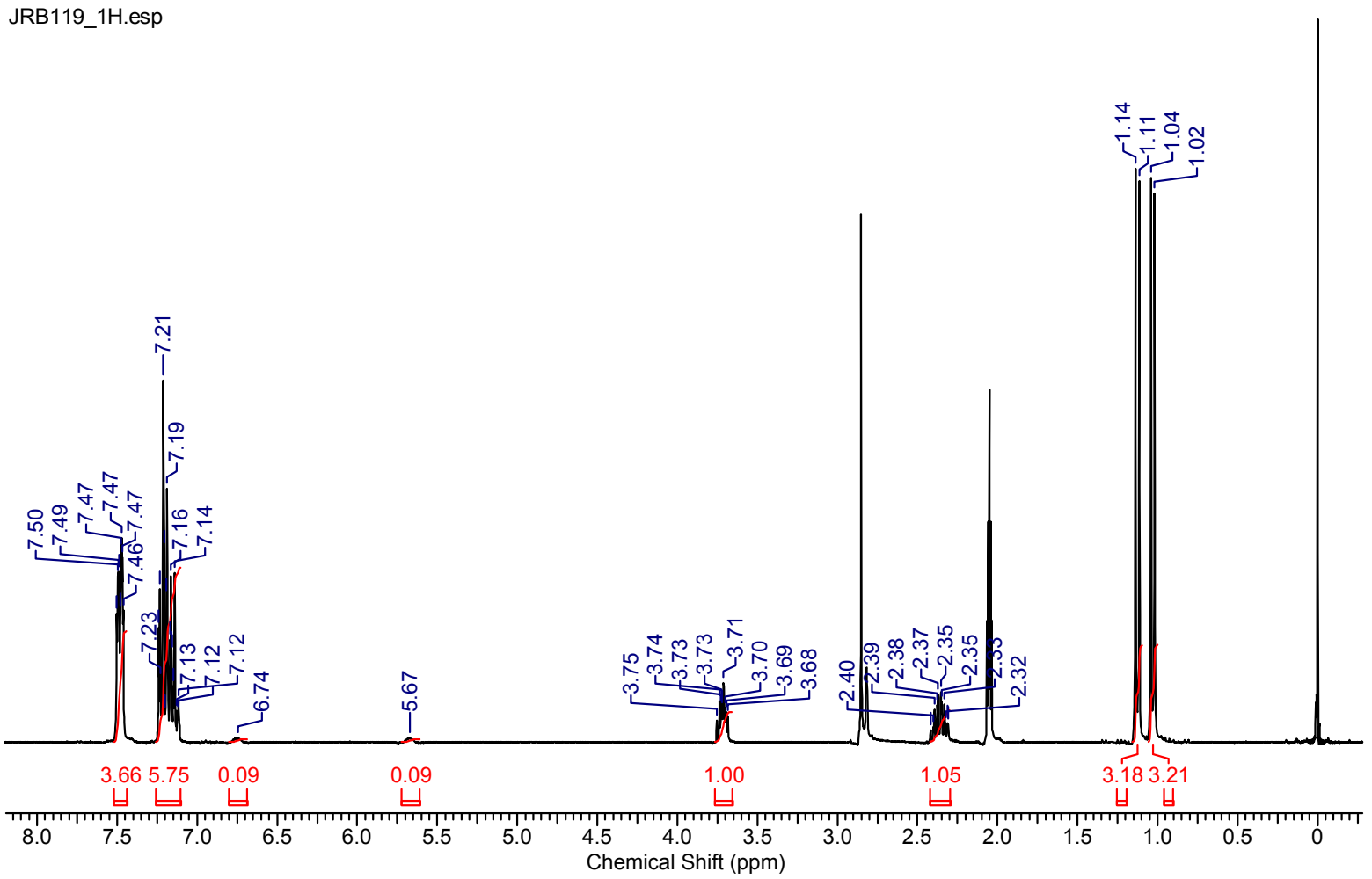
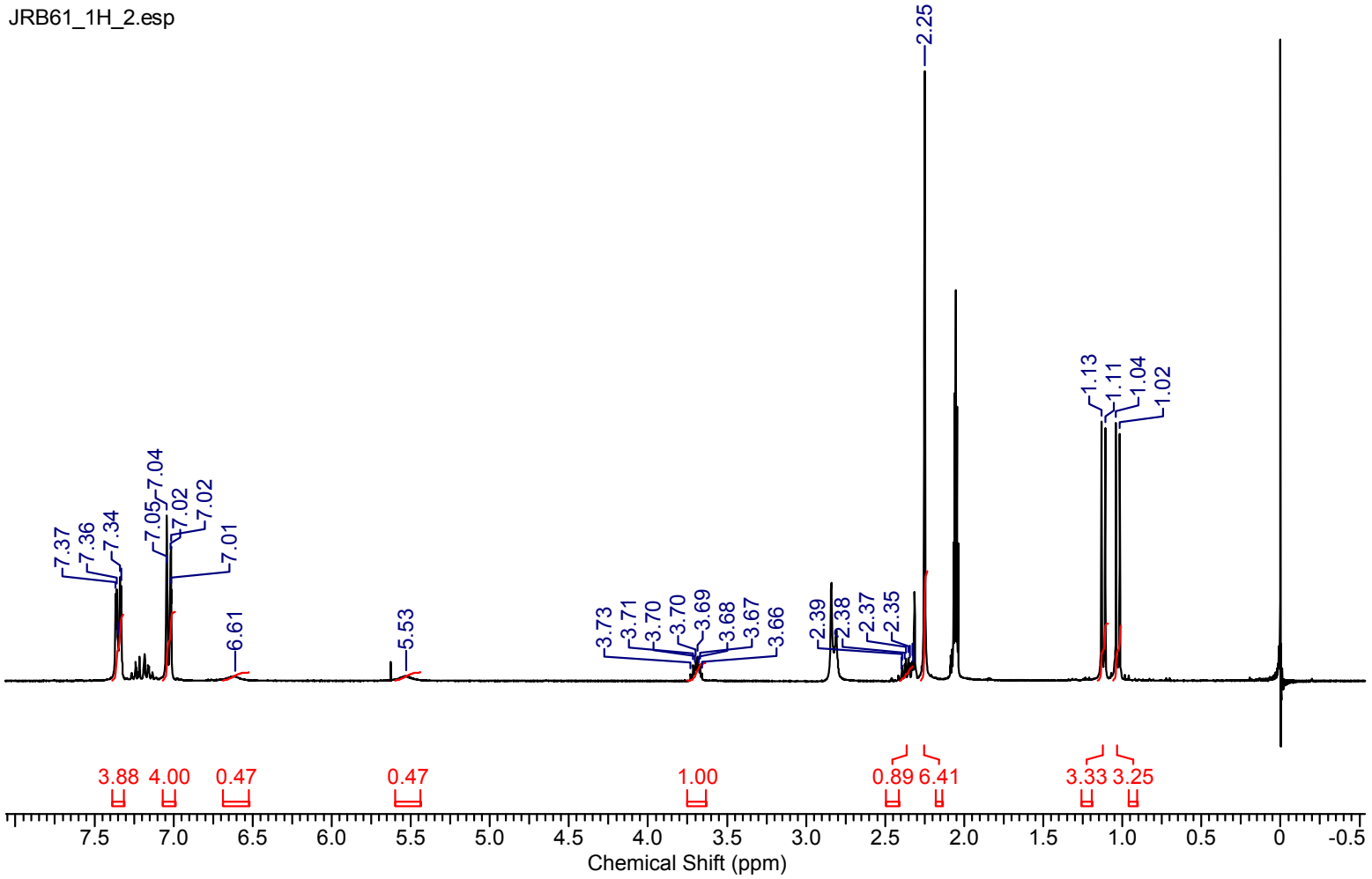


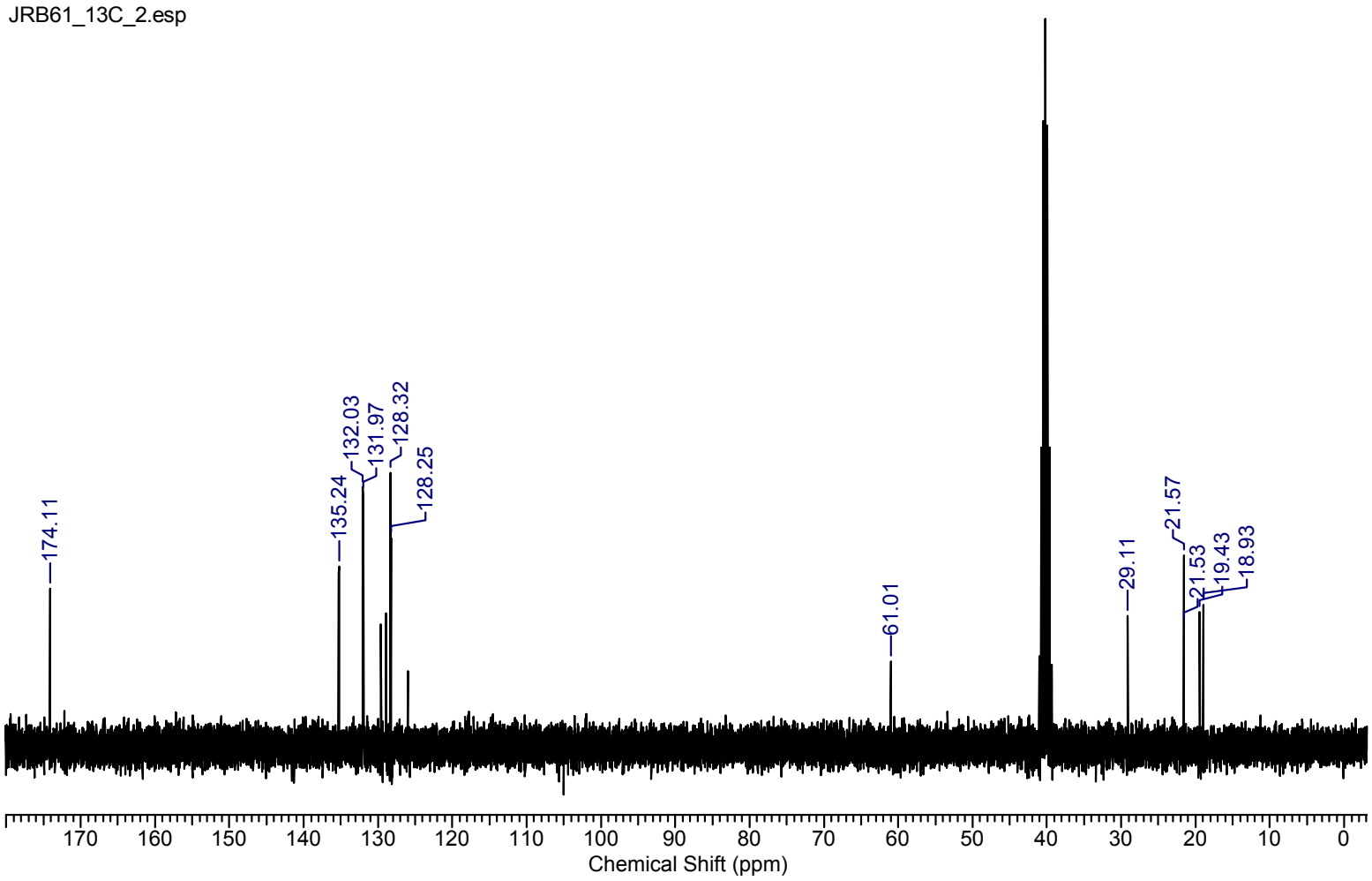
APPENDIX 9: ^{1}H NMR FOR COMPOUND 25



APPENDIX 10: ^{1}H NMR FOR COMPOUND 49A

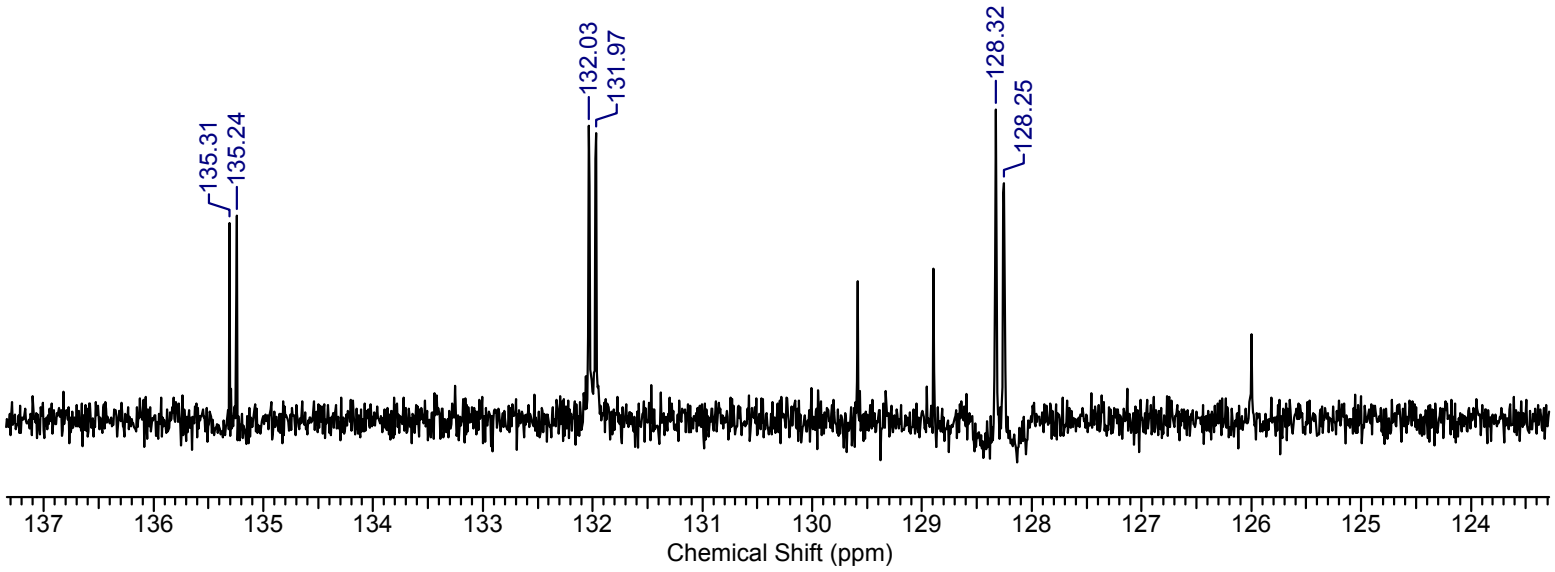


APPENDIX 11A: ^{13}C NMR FOR COMPOUND 49A

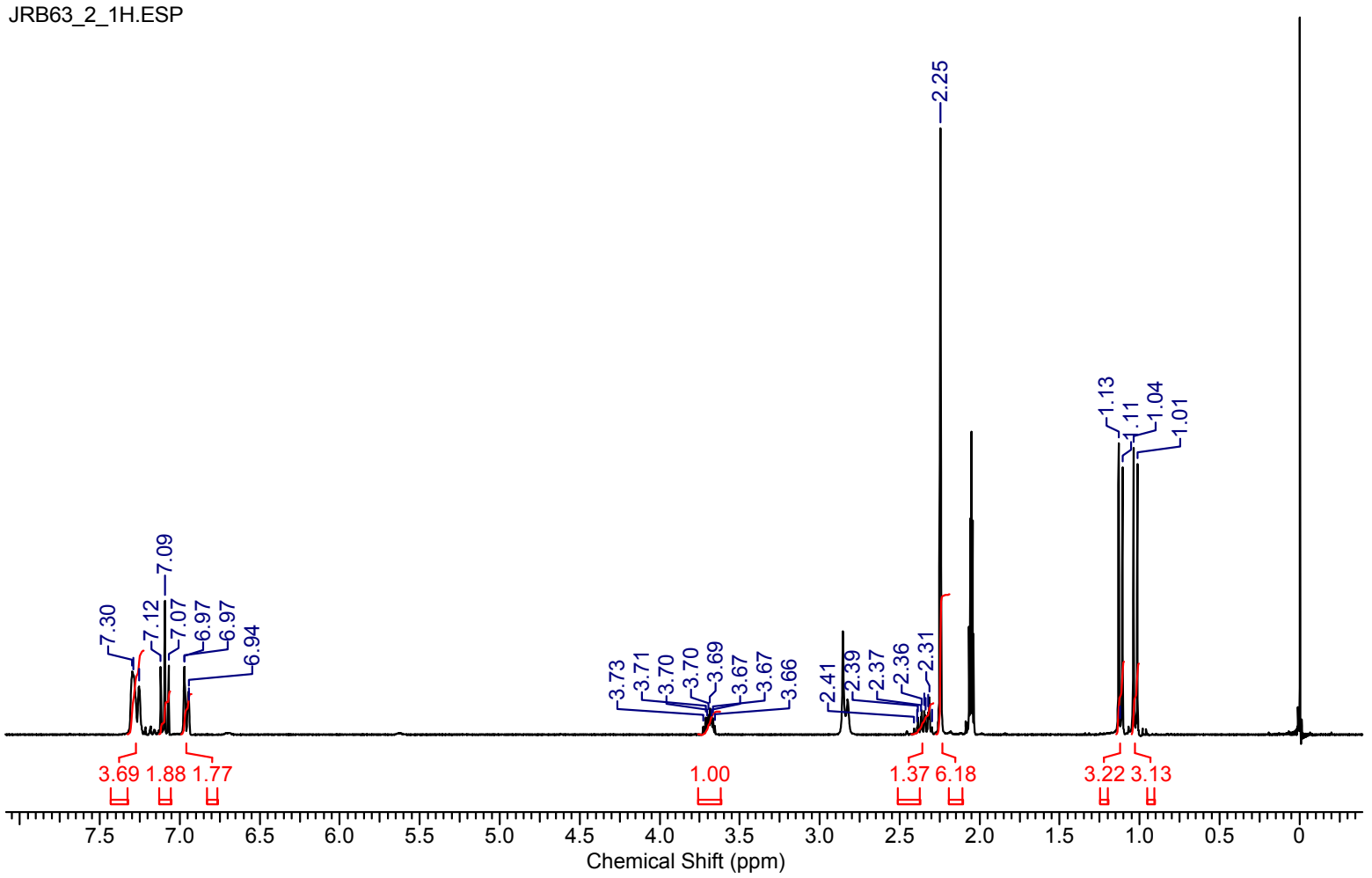


APPENDIX 11B: ^{13}C NMR CLOSE-UP FOR COMPOUND 49A

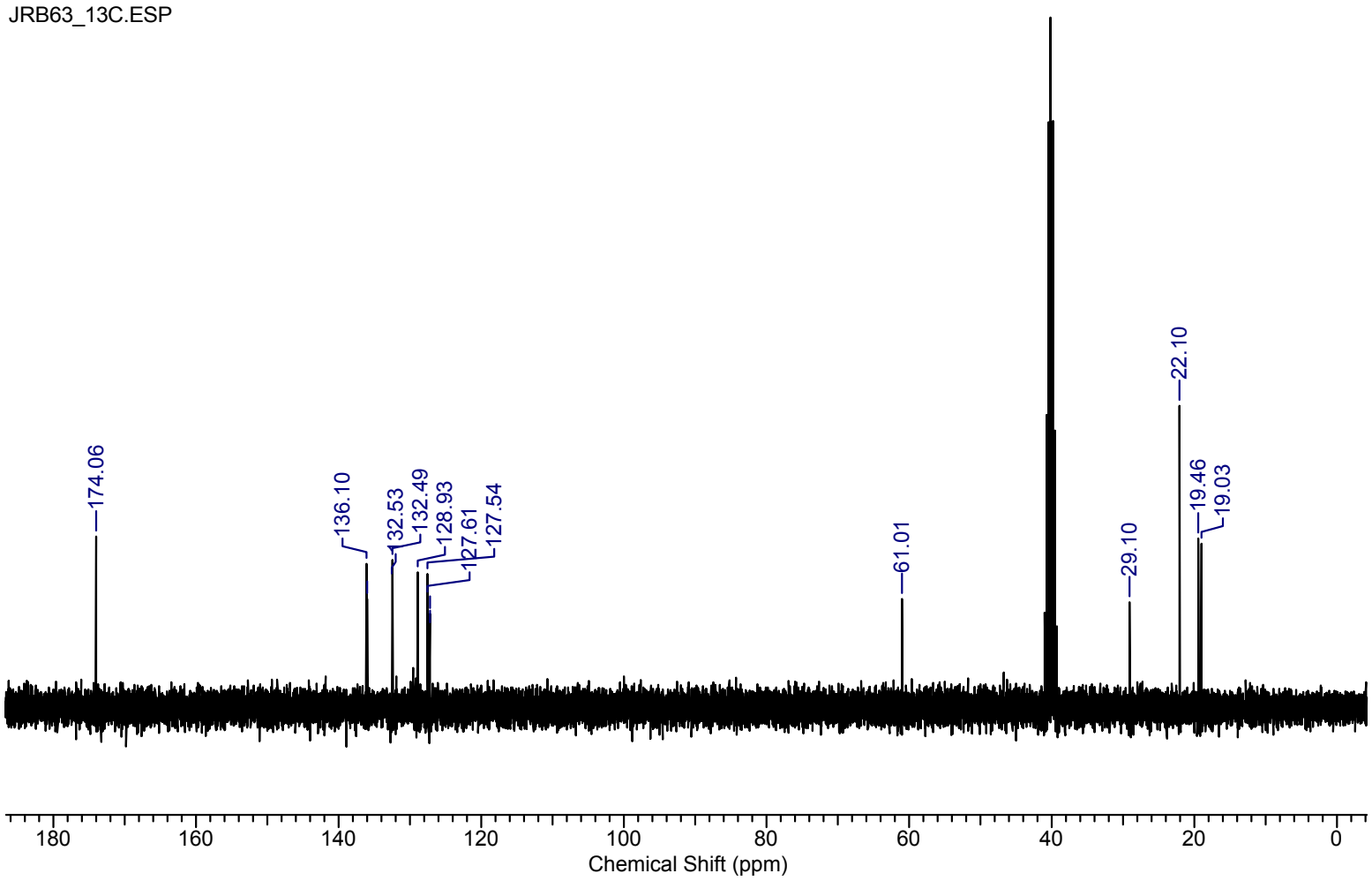
JRB61_13C_2.esp



APPENDIX 12: ^{1}H NMR FOR COMPOUND 49B

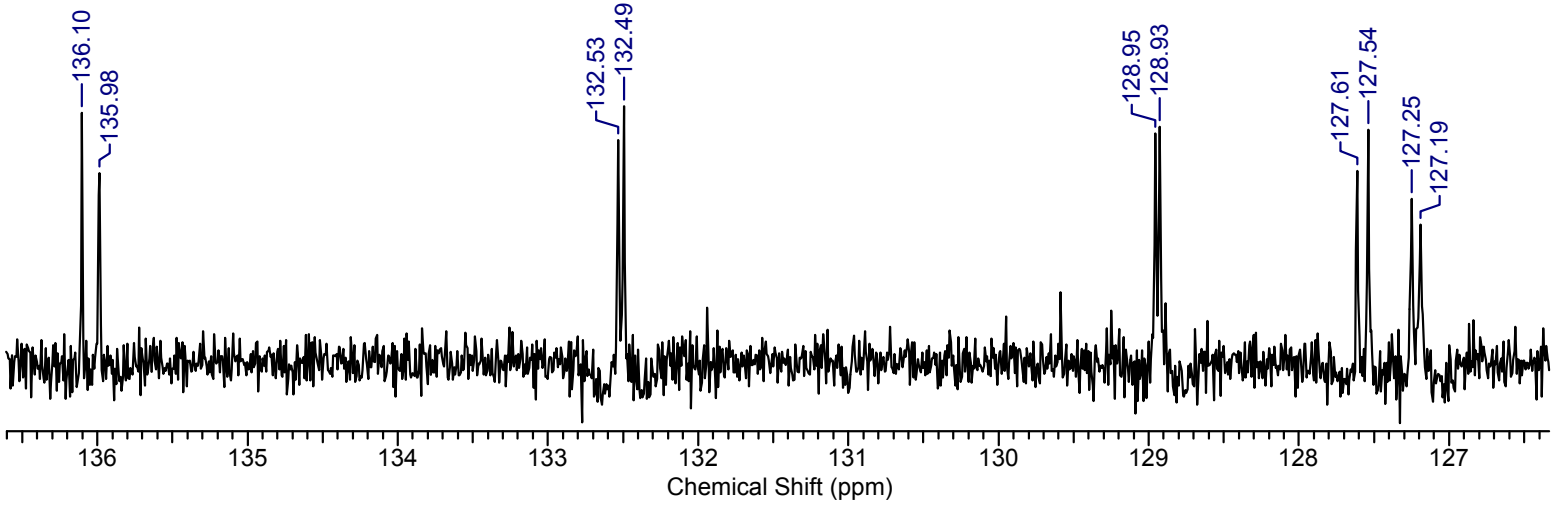


APPENDIX 13A: ^{13}C NMR FOR COMPOUND 49B

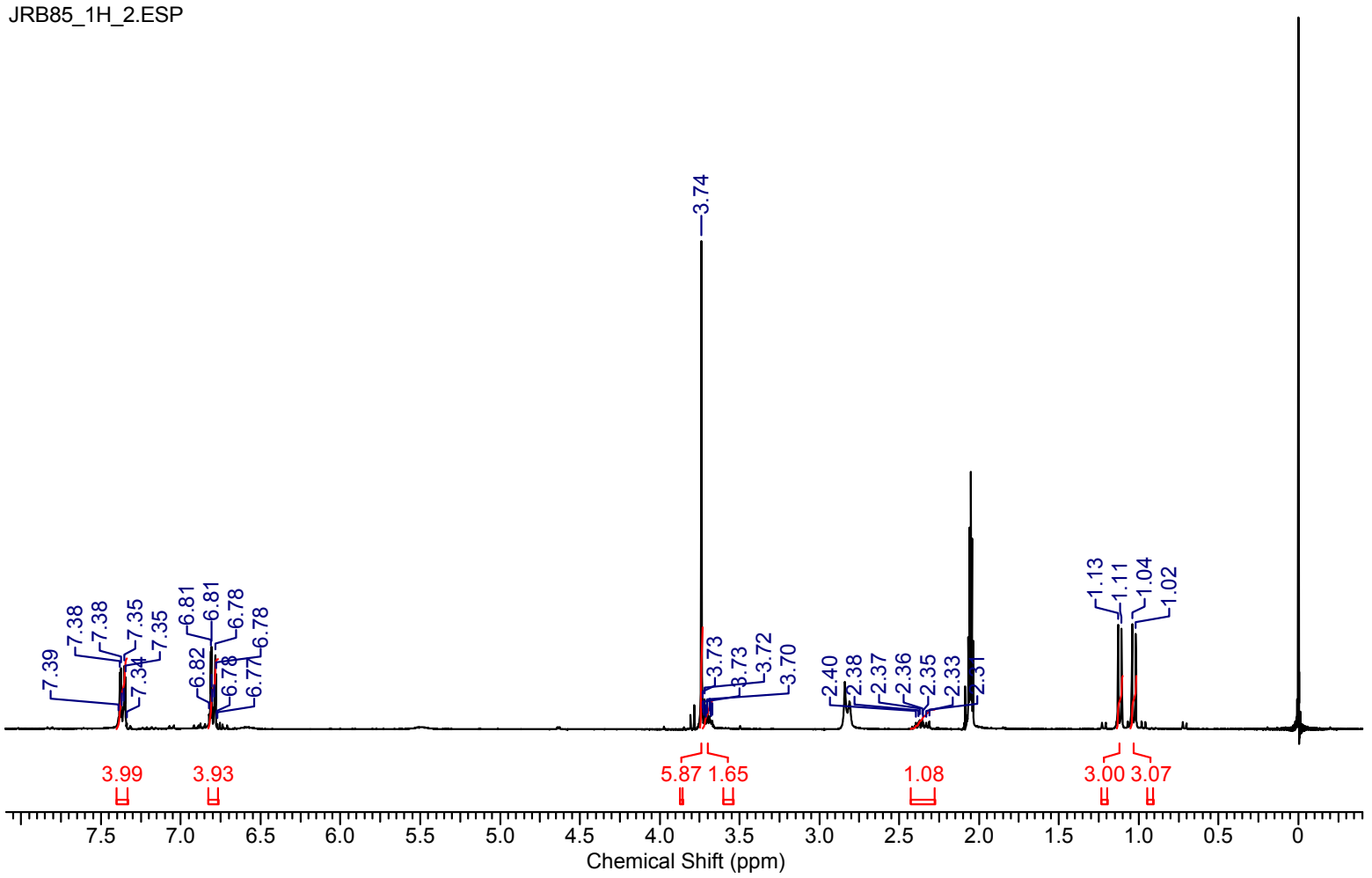


APPENDIX 13B: ^{13}C NMR CLOSE-UP FOR COMPOUND 49B

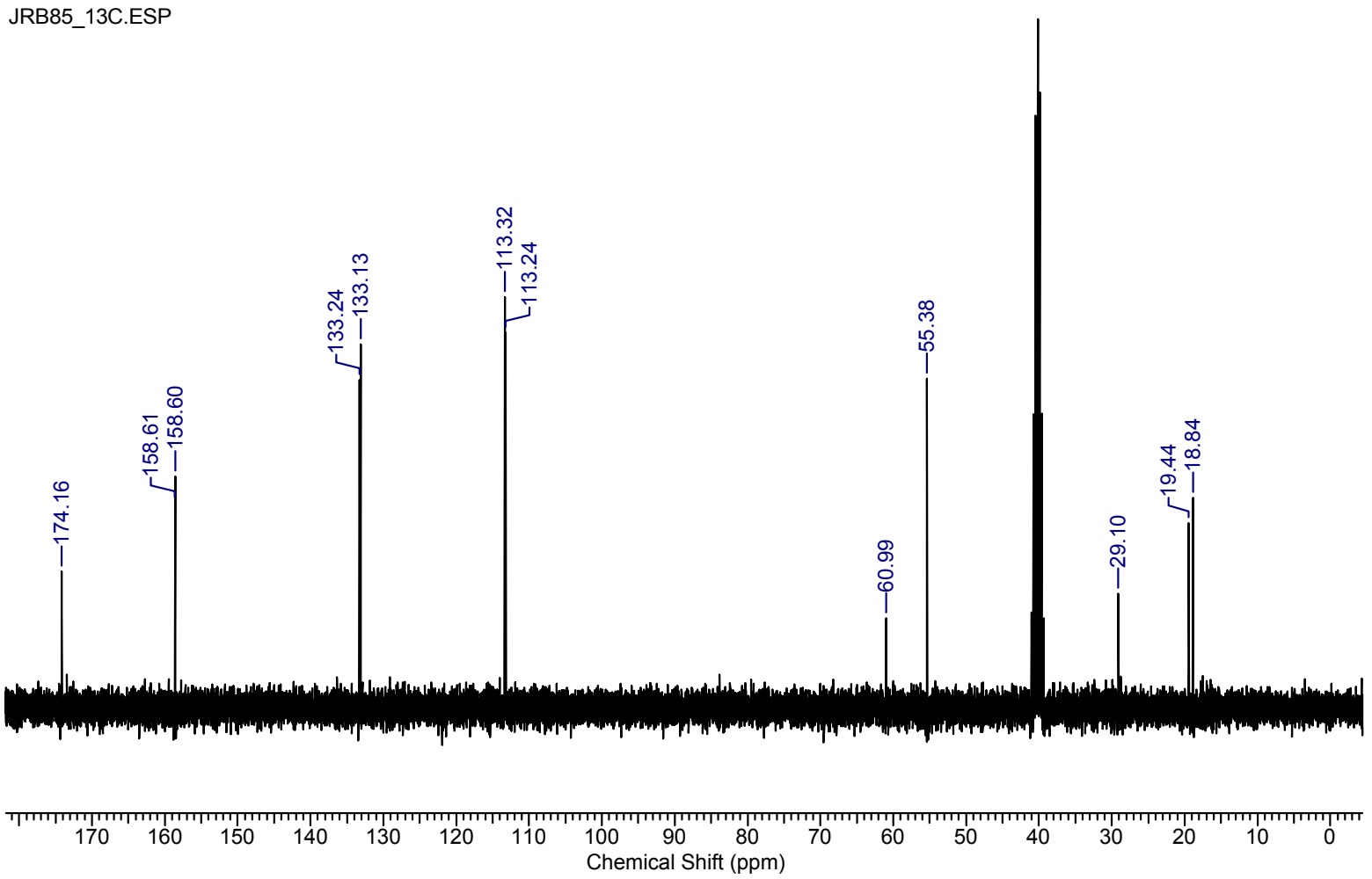
JRB63_13C.esp



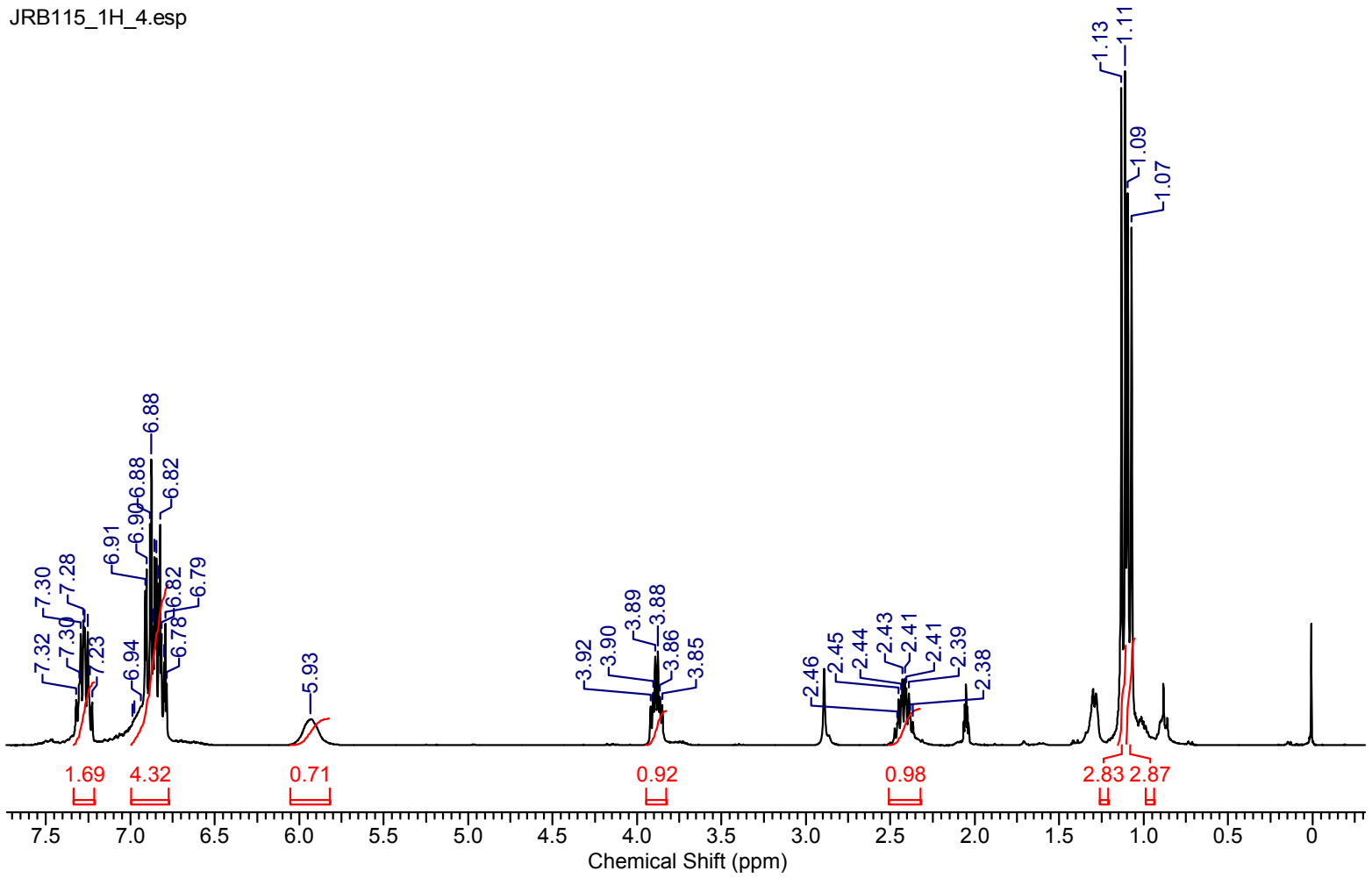
APPENDIX 14: ^{1}H NMR FOR COMPOUND 49C



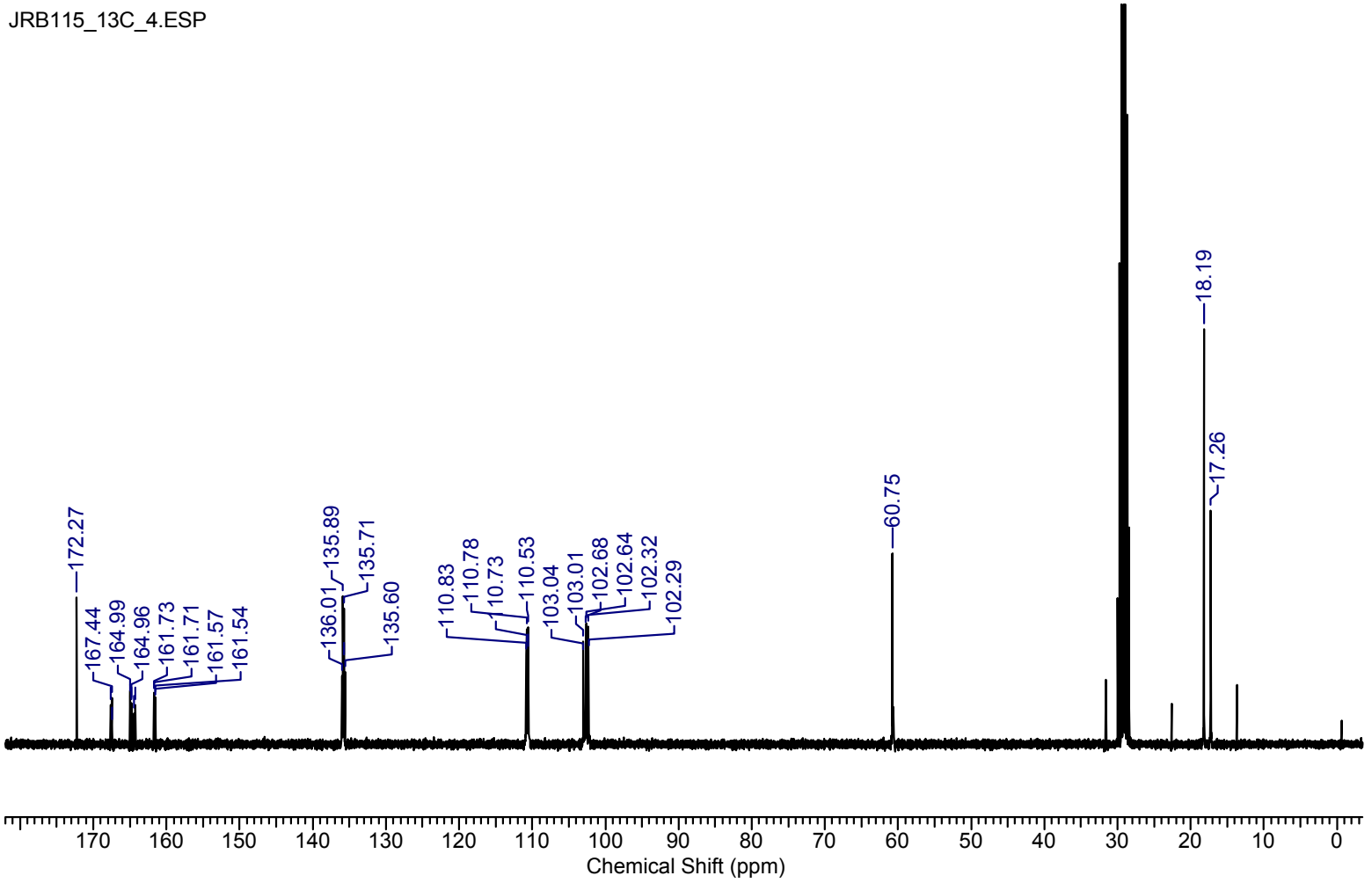
APPENDIX 15: ^{13}C NMR FOR COMPOUND 49C



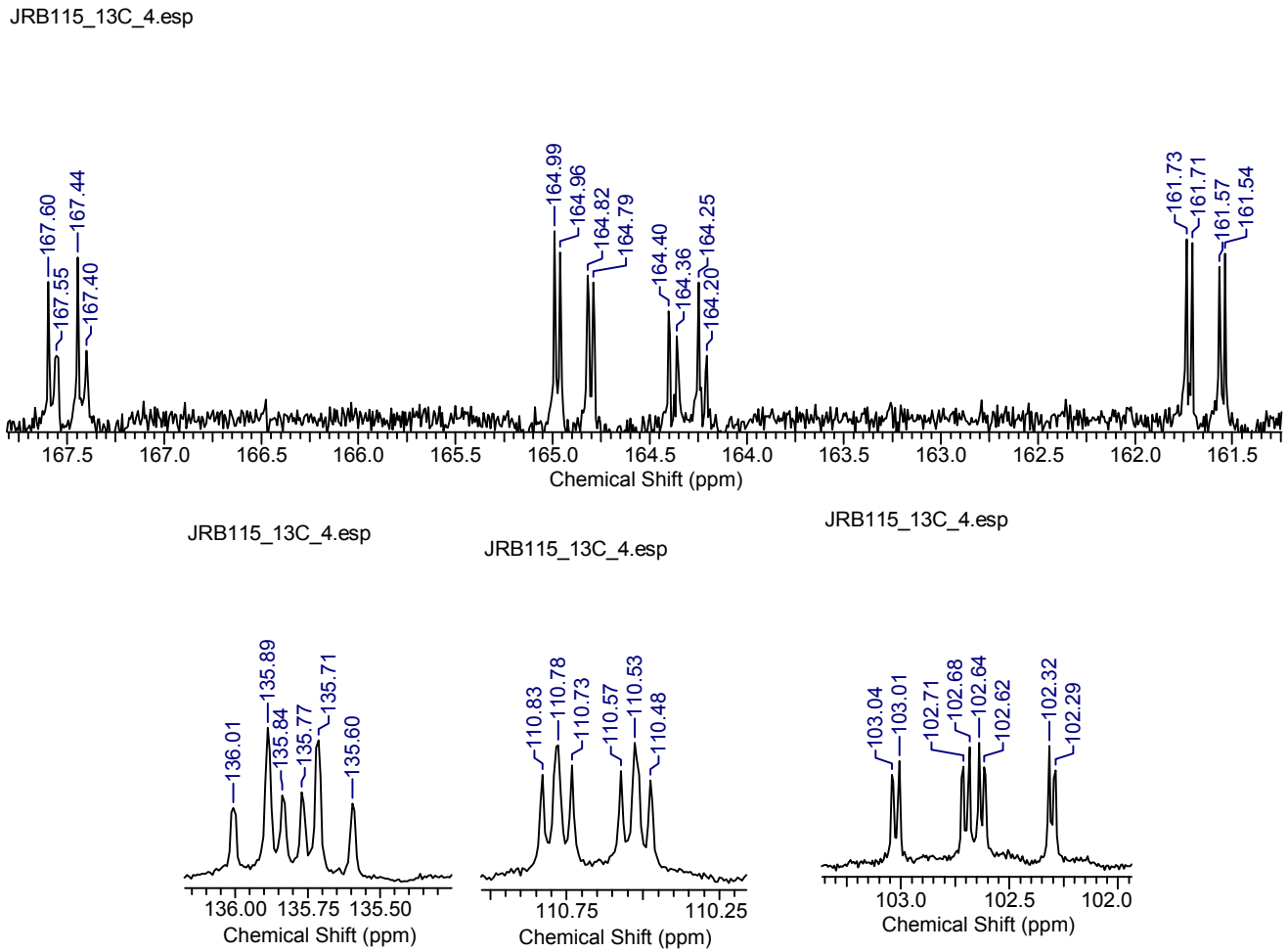
APPENDIX 16: ^{1}H NMR FOR COMPOUND 49D



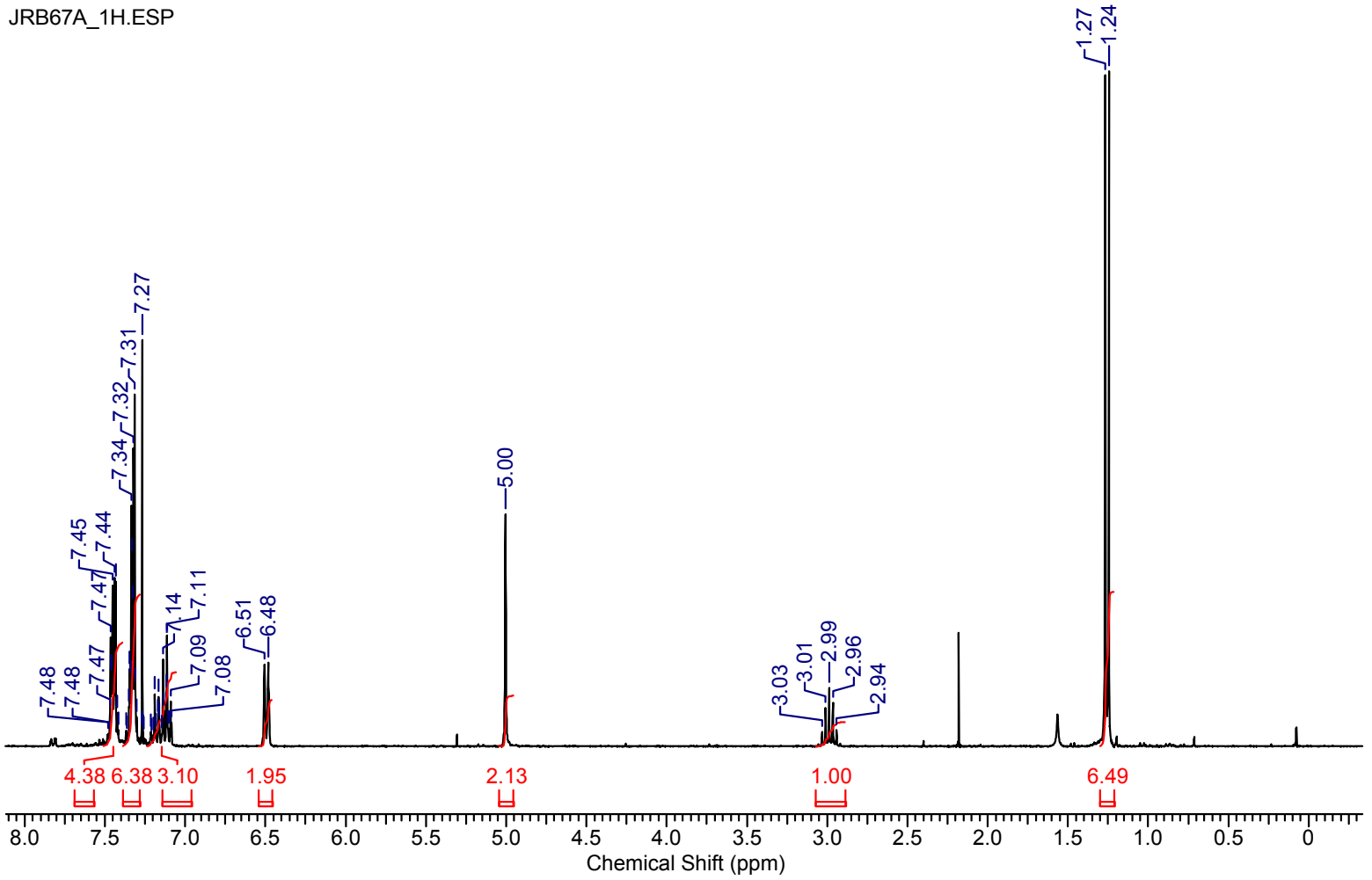
APPENDIX 17A: ^{13}C NMR FOR COMPOUND 49D



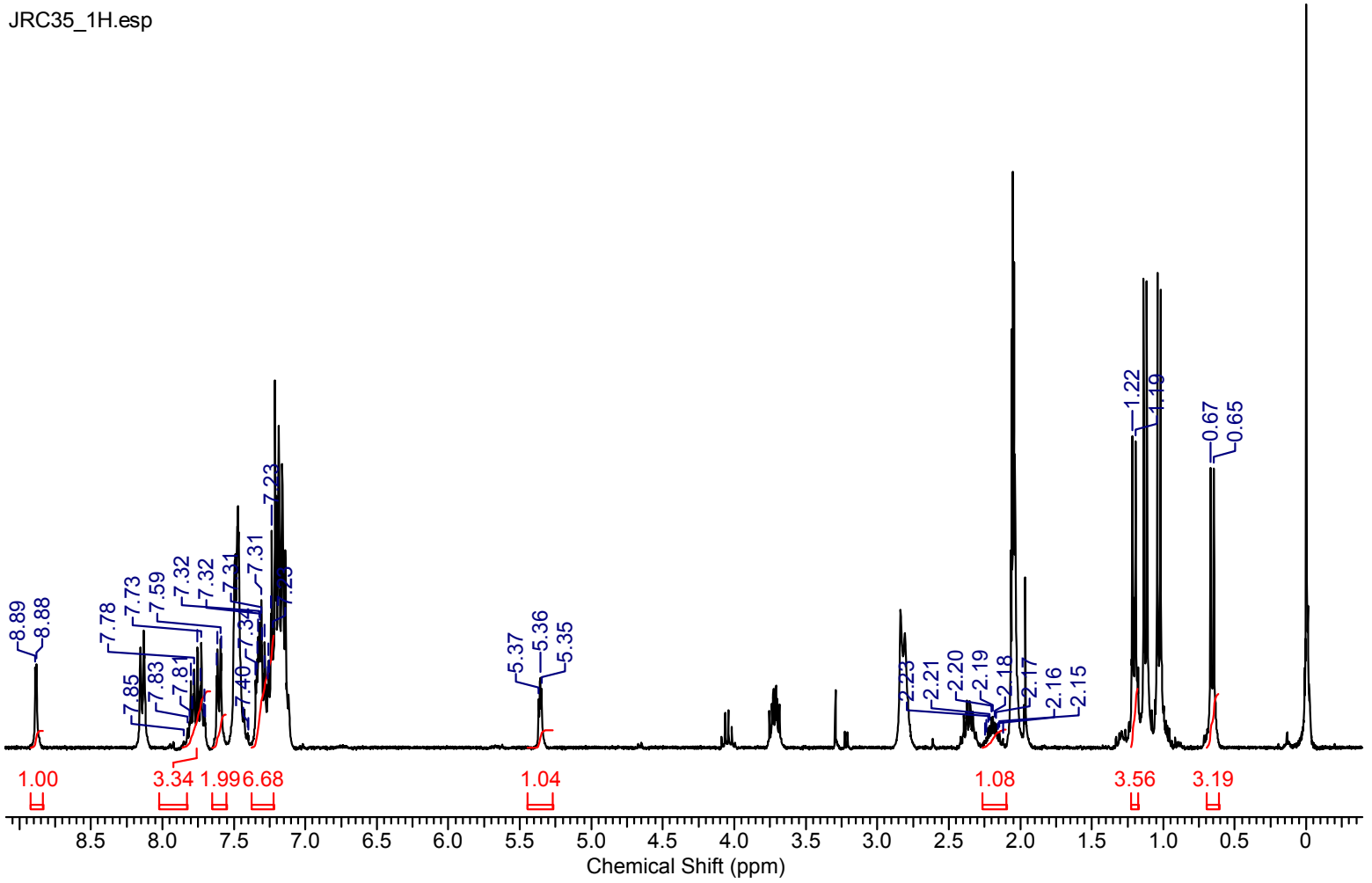
APPENDIX 17B: ^{13}C NMR CLOSE-UPS FOR COMPOUND 49D



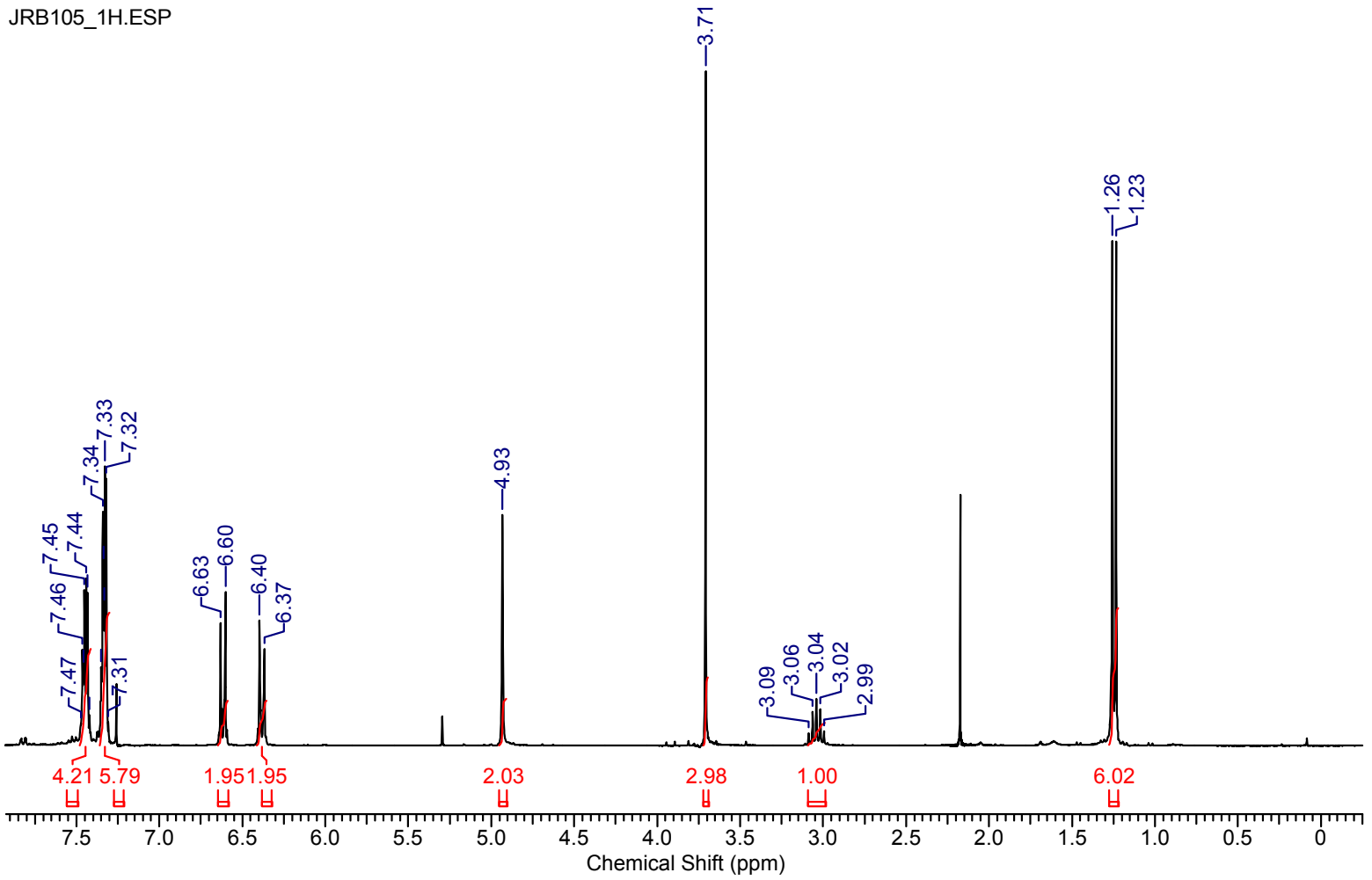
APPENDIX 18: ^{1}H NMR FOR COMPOUND 65A



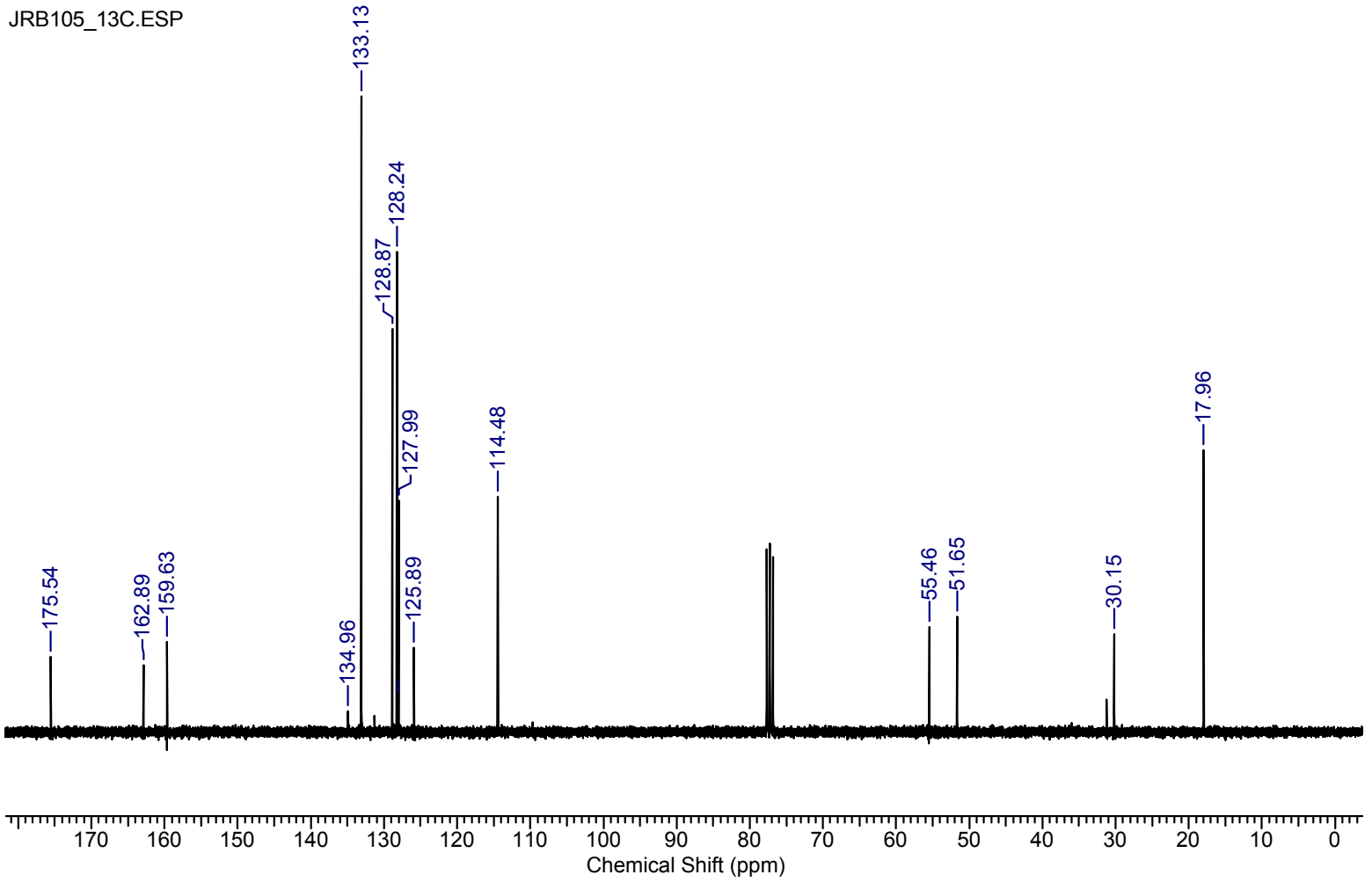
APPENDIX 19: ^{1}H NMR FOR COMPOUND 65B



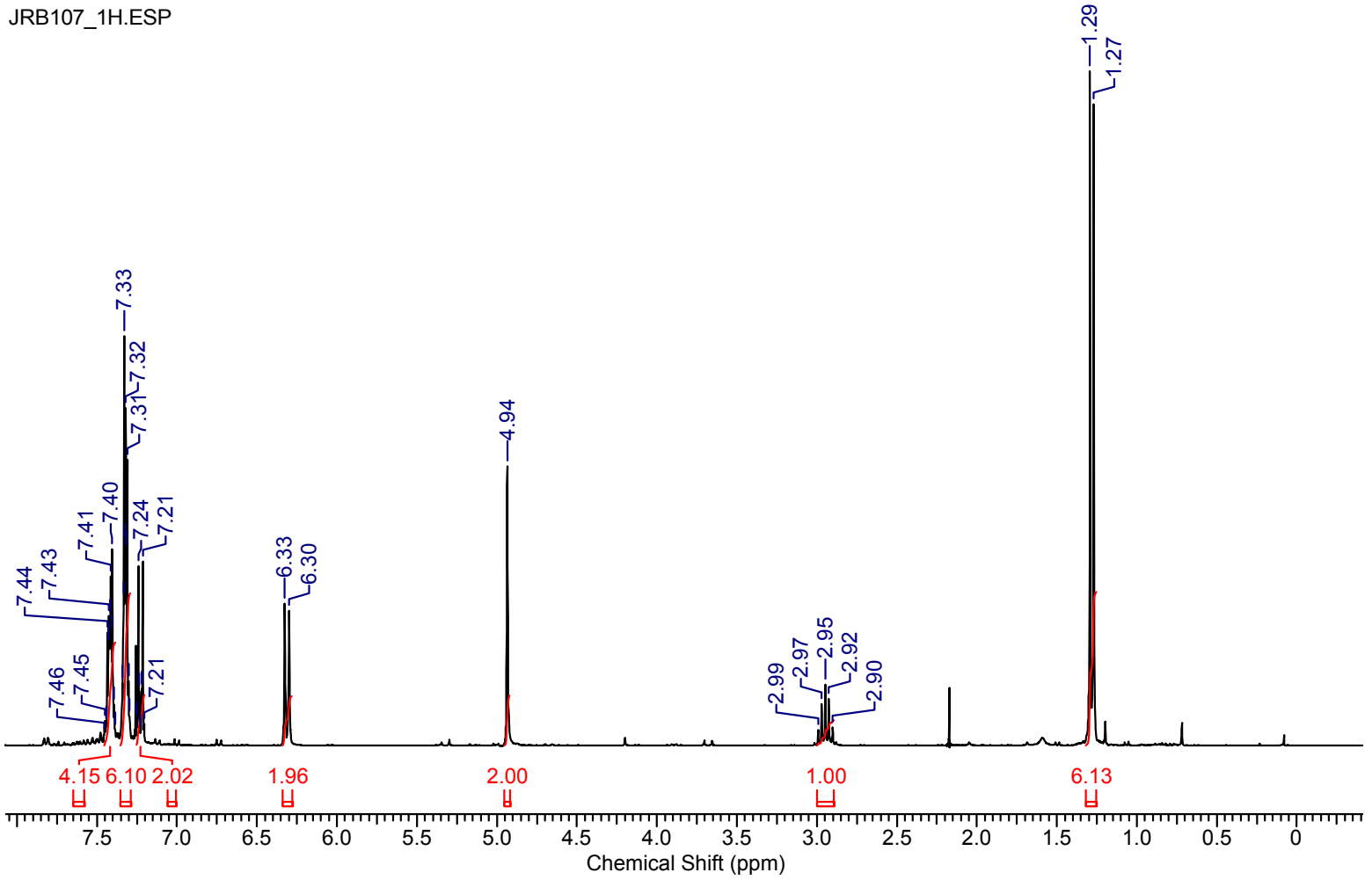
APPENDIX 20: ^{1}H NMR FOR COMPOUND 67A



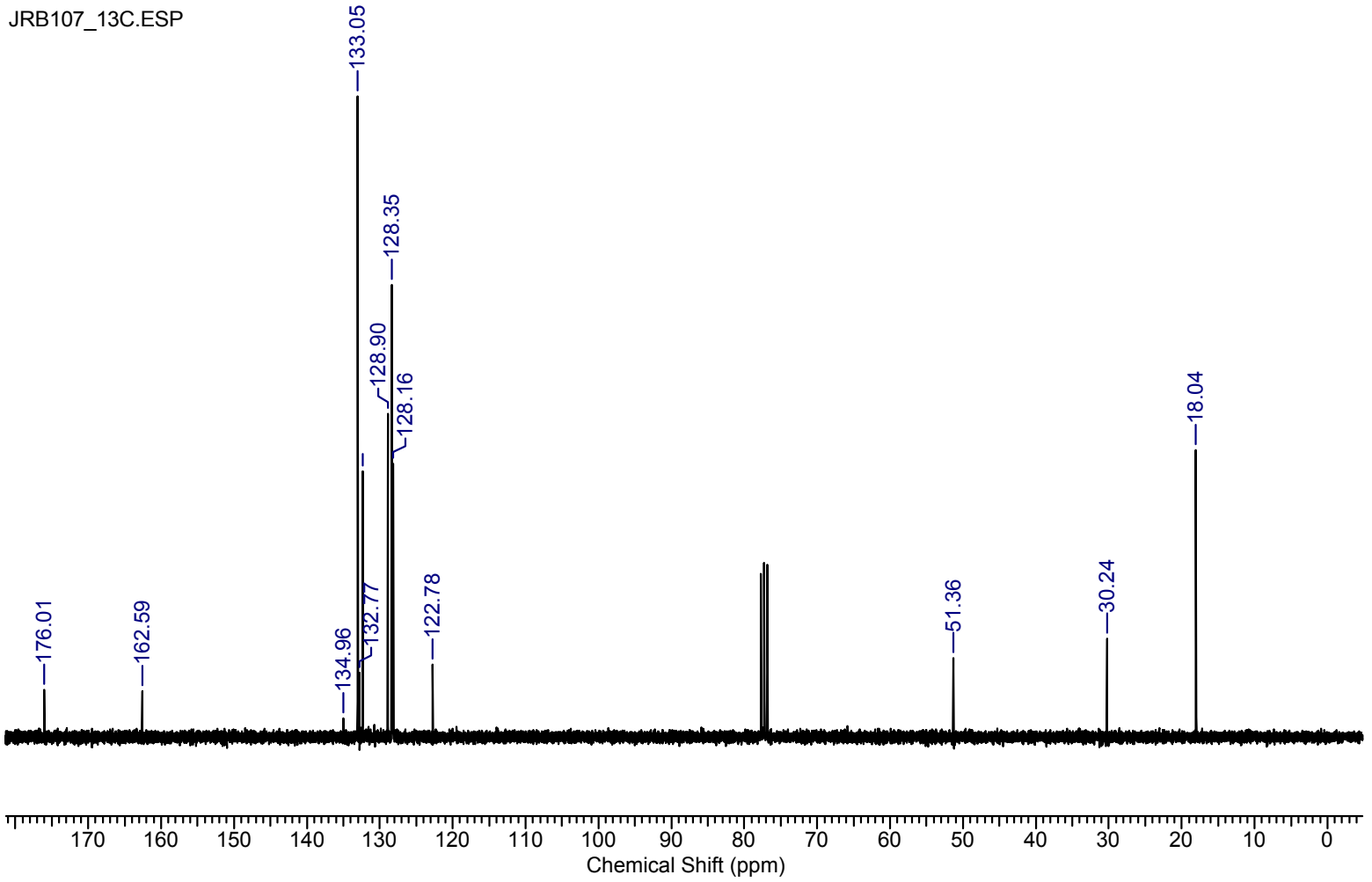
APPENDIX 21: ^{13}C NMR FOR COMPOUND 67A



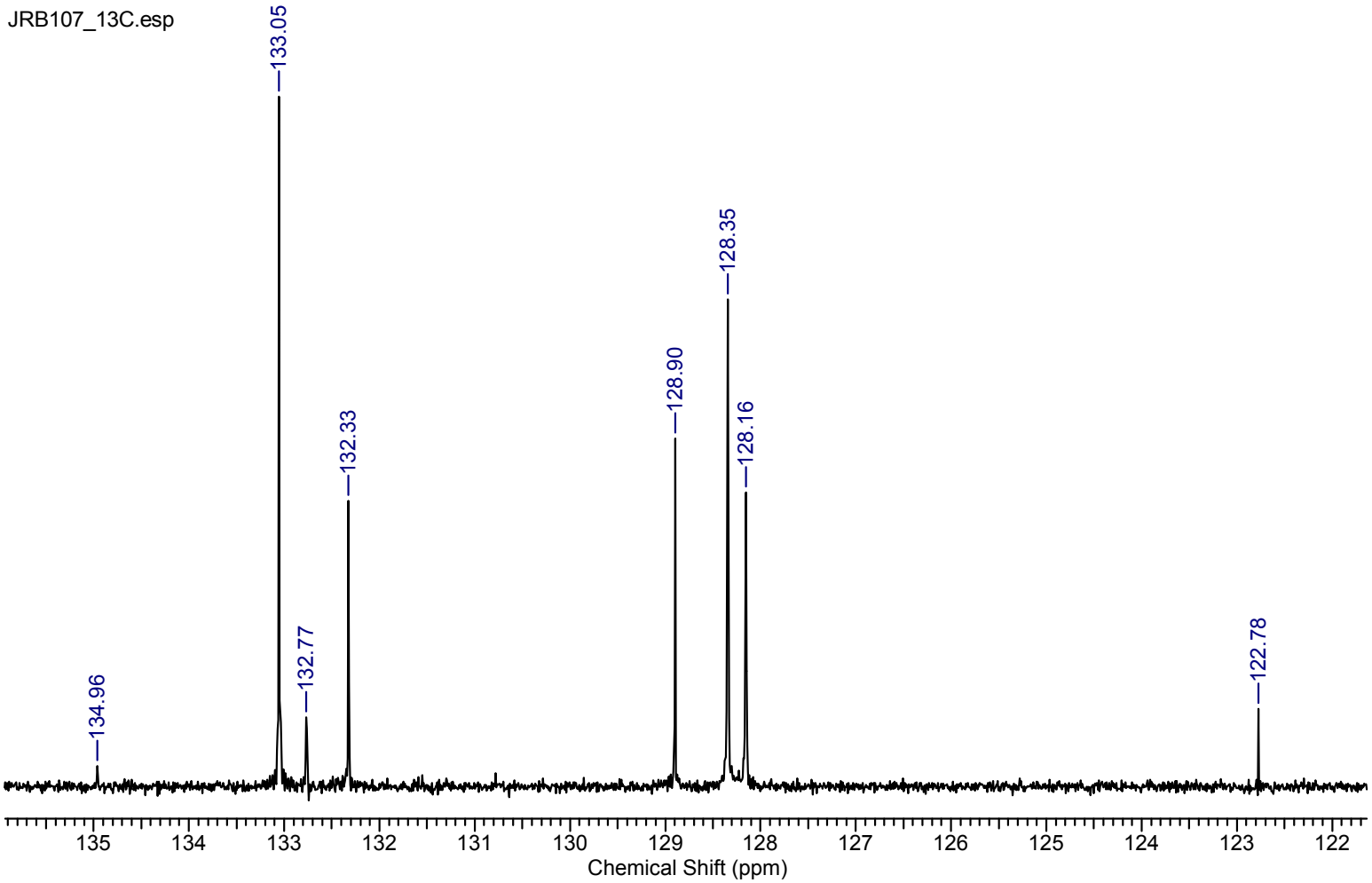
APPENDIX 22: ^{1}H NMR FOR COMPOUND 67B



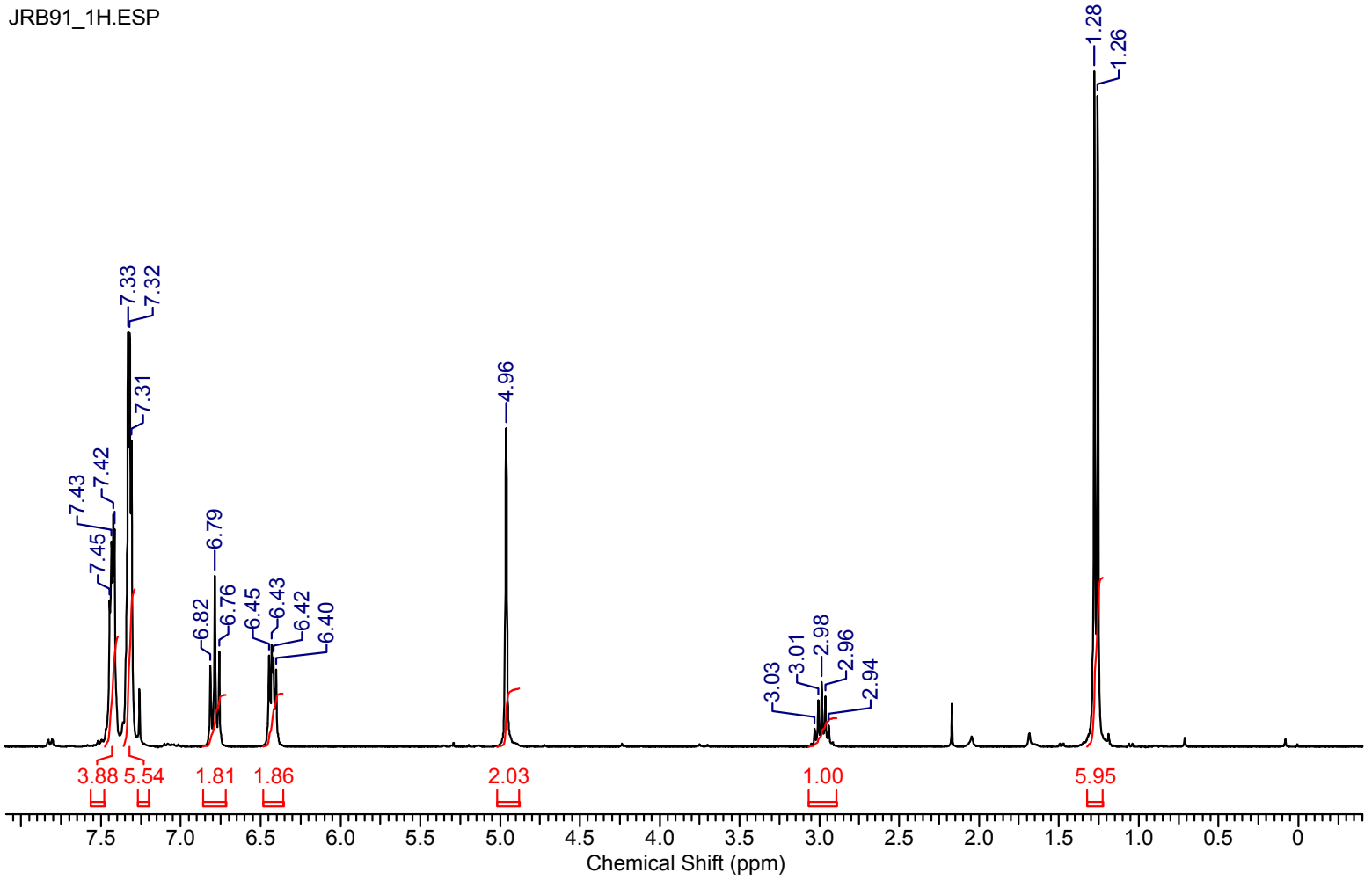
APPENDIX 23A: ^{13}C NMR FOR COMPOUND 67B



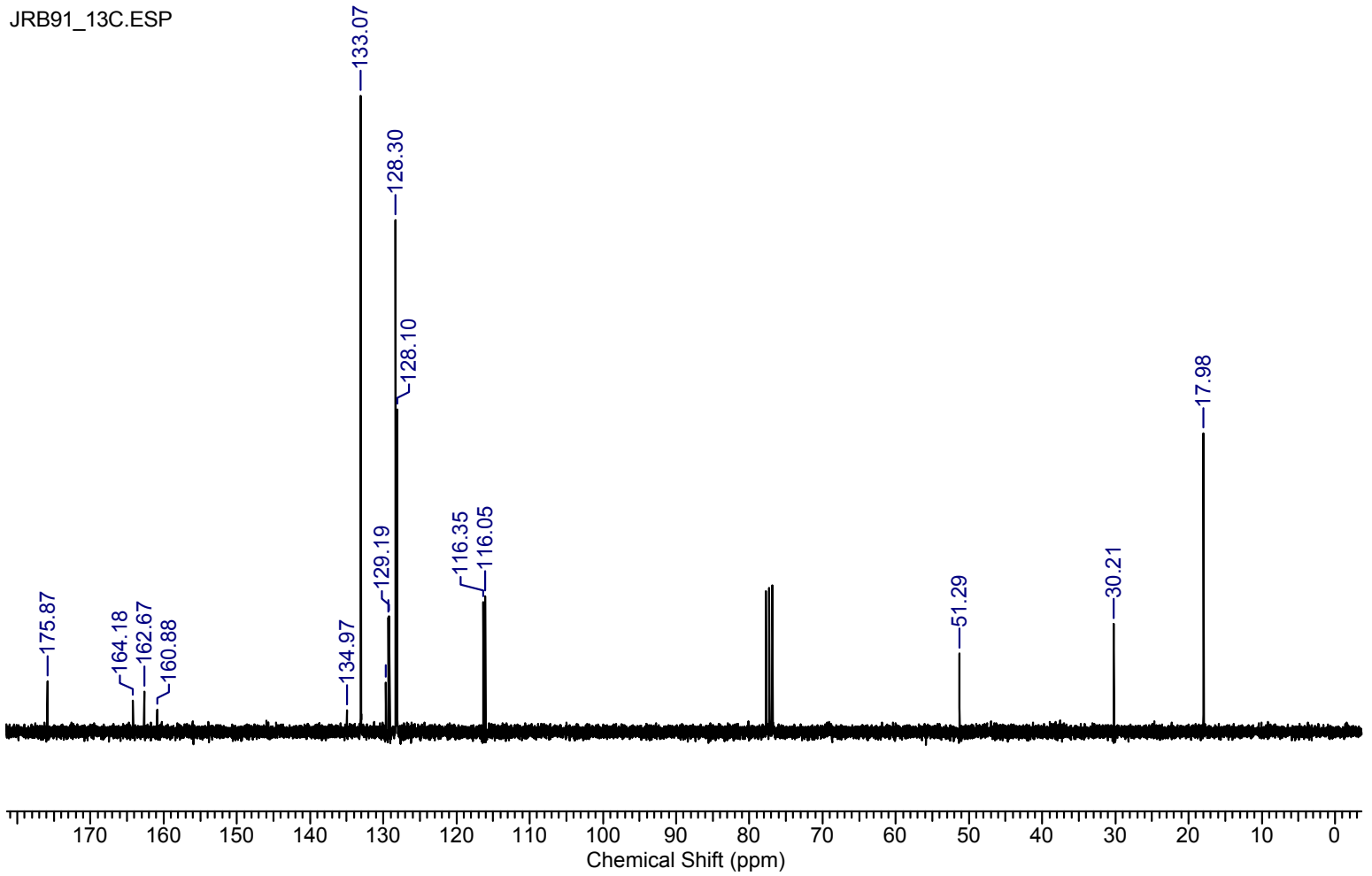
APPENDIX 23B: ^{13}C NMR CLOSE-UP FOR COMPOUND 67B



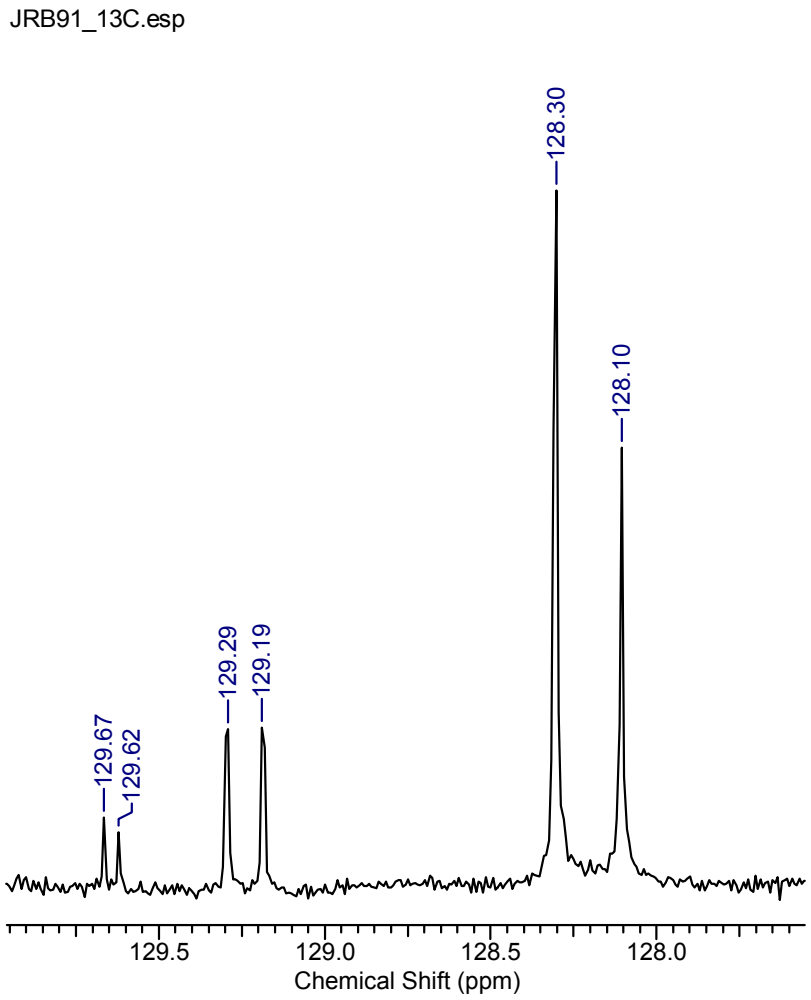
APPENDIX 24: ^{1}H NMR FOR COMPOUND 67C

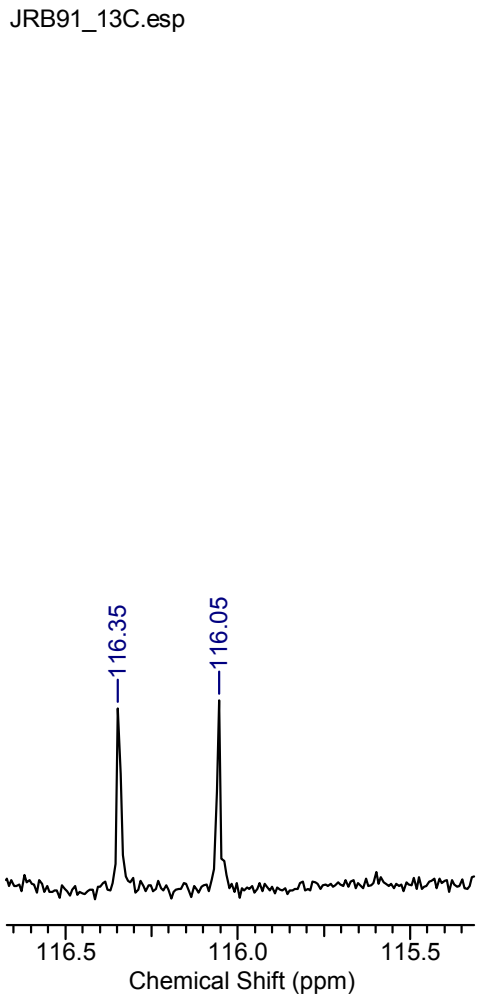


APPENDIX 25A: ^{13}C NMR FOR COMPOUND 67C

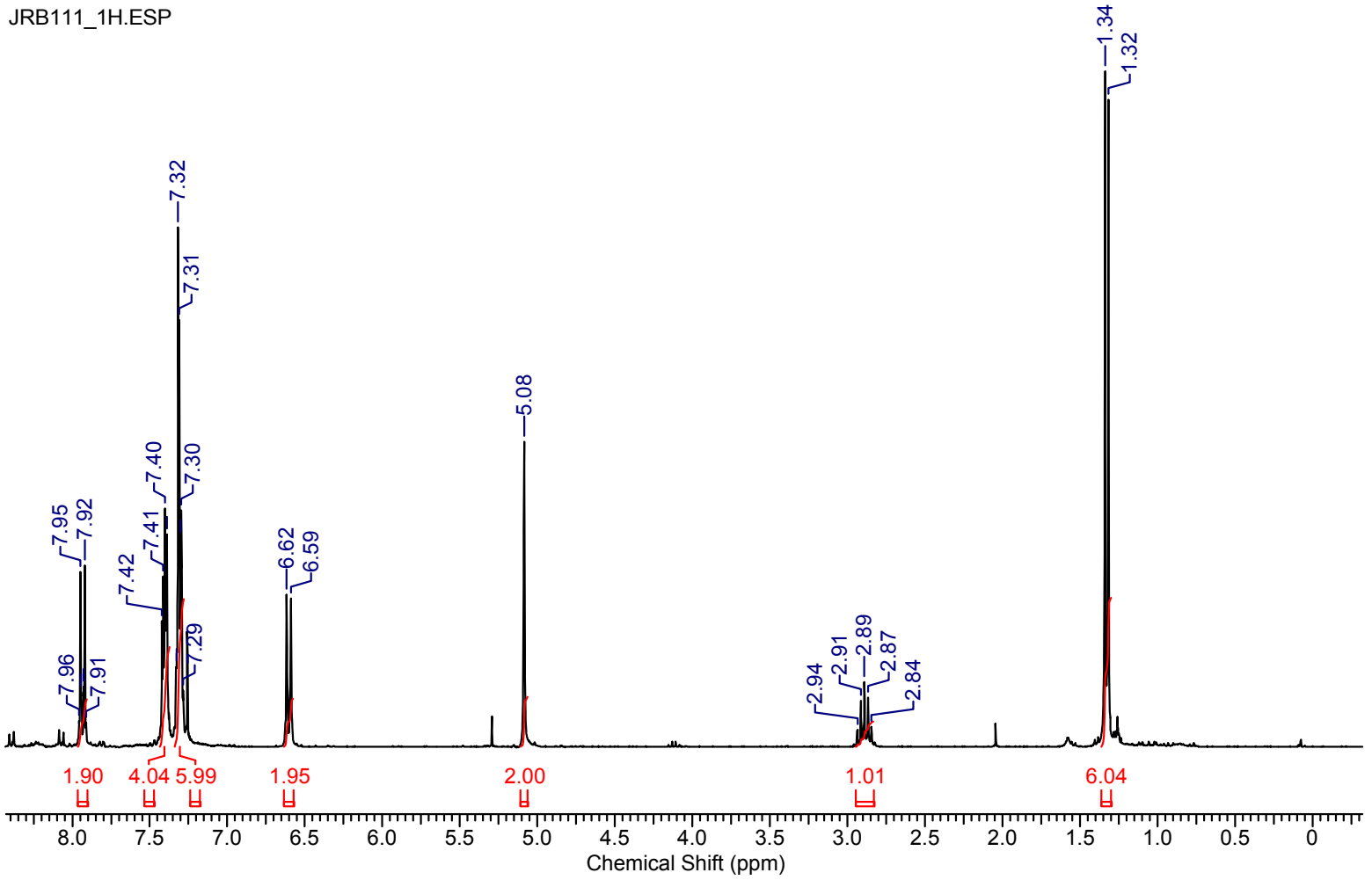


APPENDIX 25B: ^{13}C NMR CLOSE-UPS FOR COMPOUND 67C

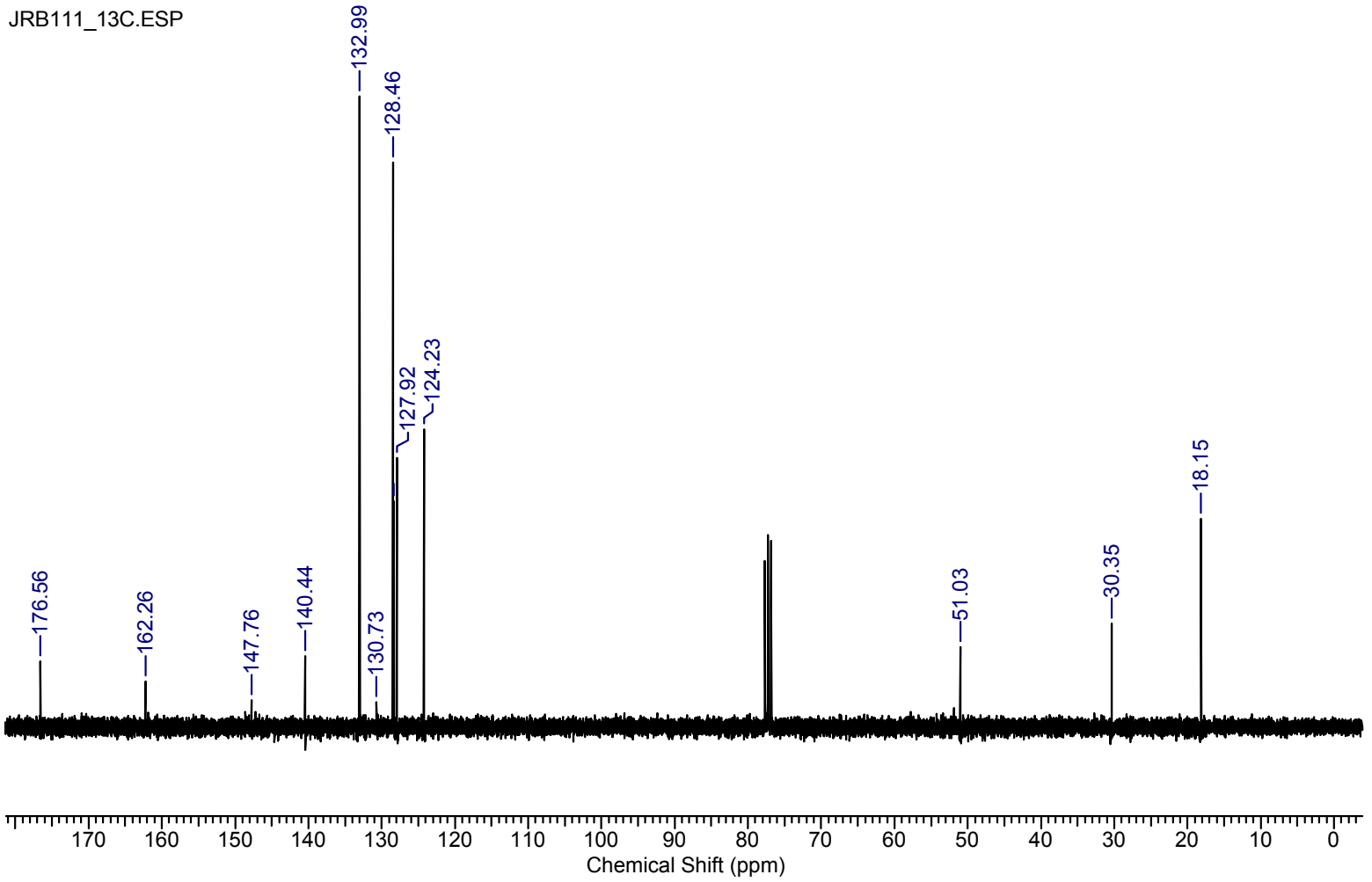




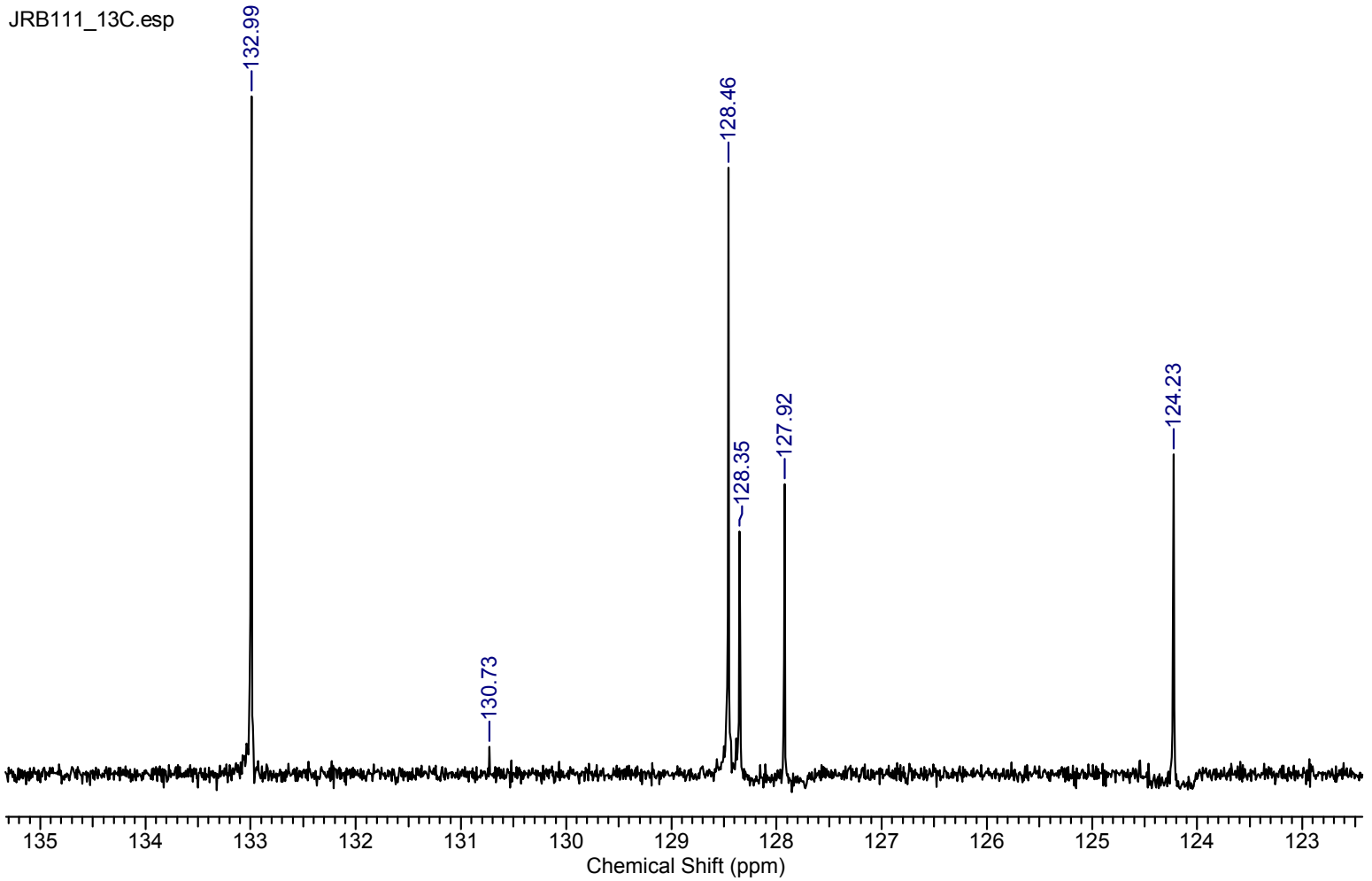
APPENDIX 26: ^{1}H NMR FOR COMPOUND 67E



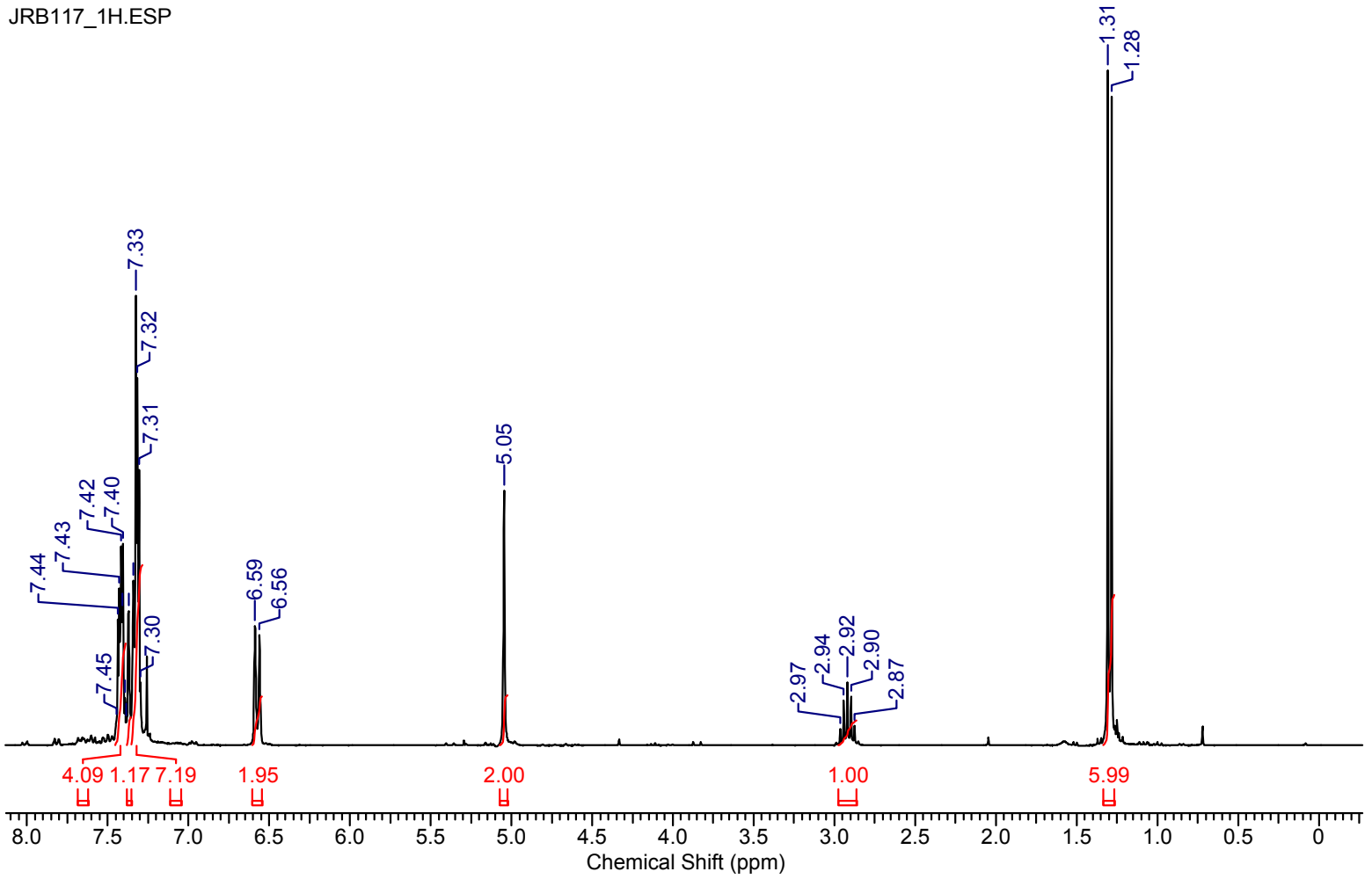
APPENDIX 27A: ^{13}C NMR FOR COMPOUND 67E



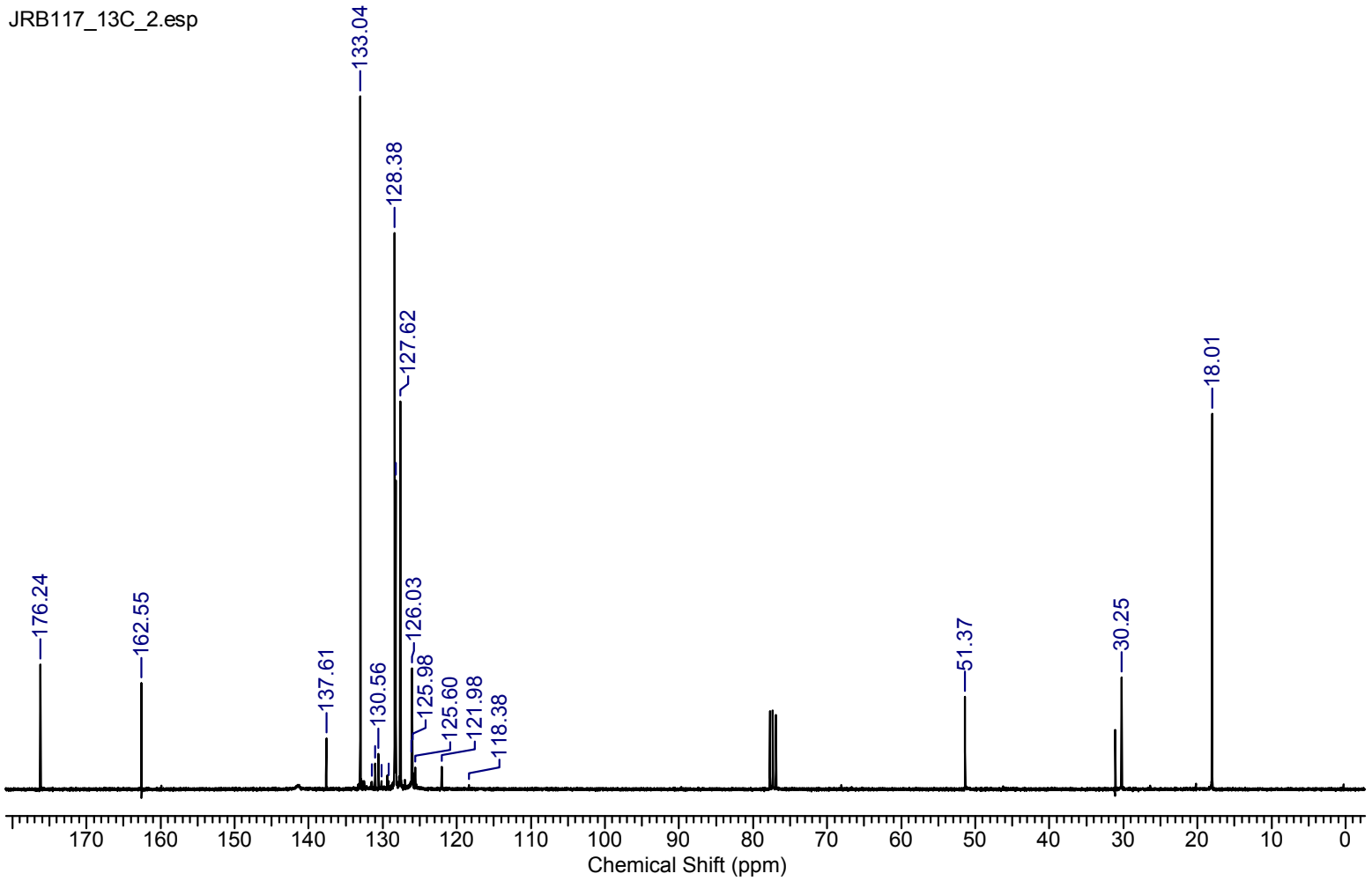
APPENDIX 27B: ^{13}C NMR CLOSE-UP FOR COMPOUND 67E



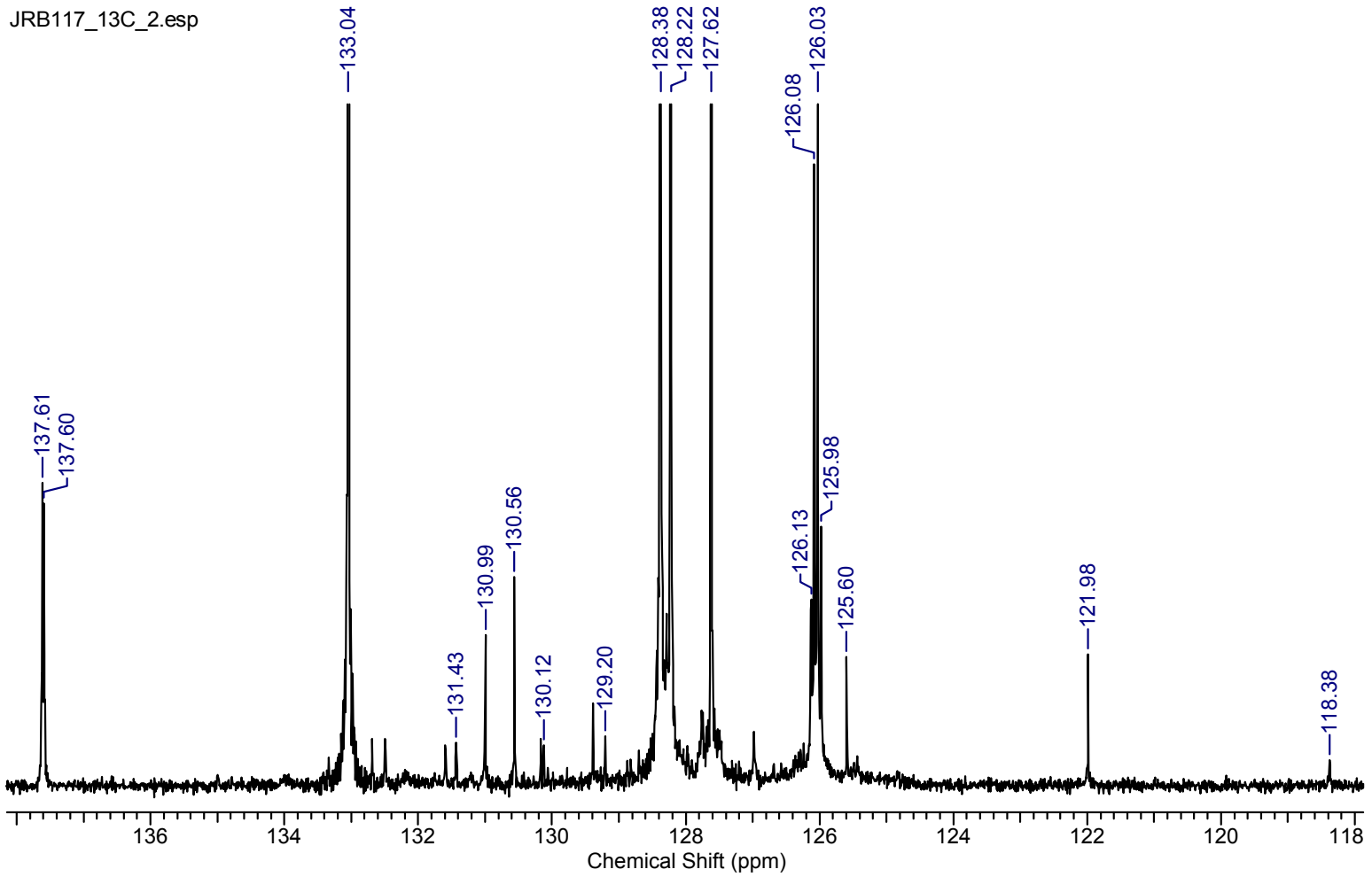
APPENDIX 28: ^{1}H NMR FOR COMPOUND 67F



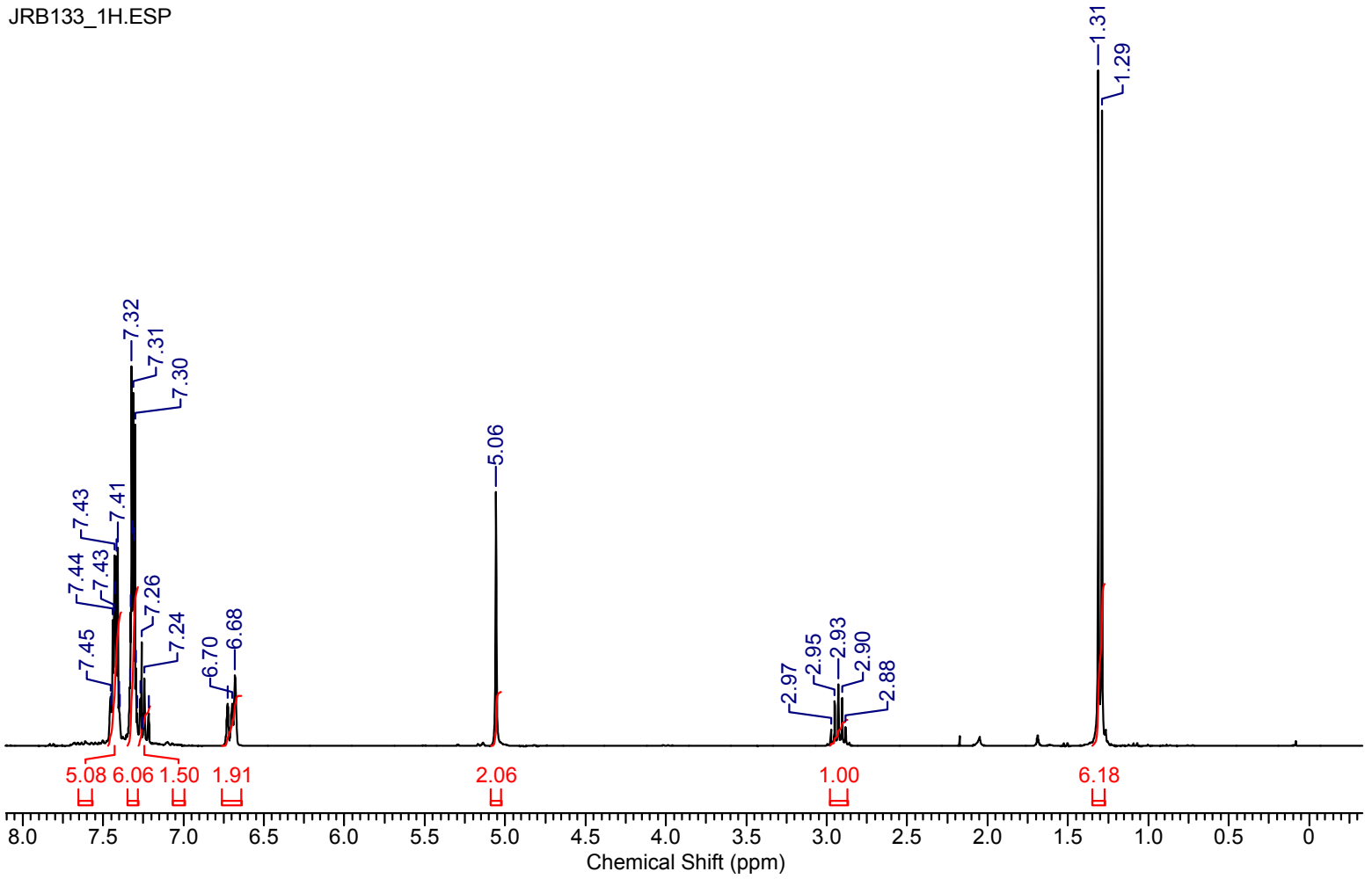
APPENDIX 29A: ^{13}C NMR FOR COMPOUND 67F



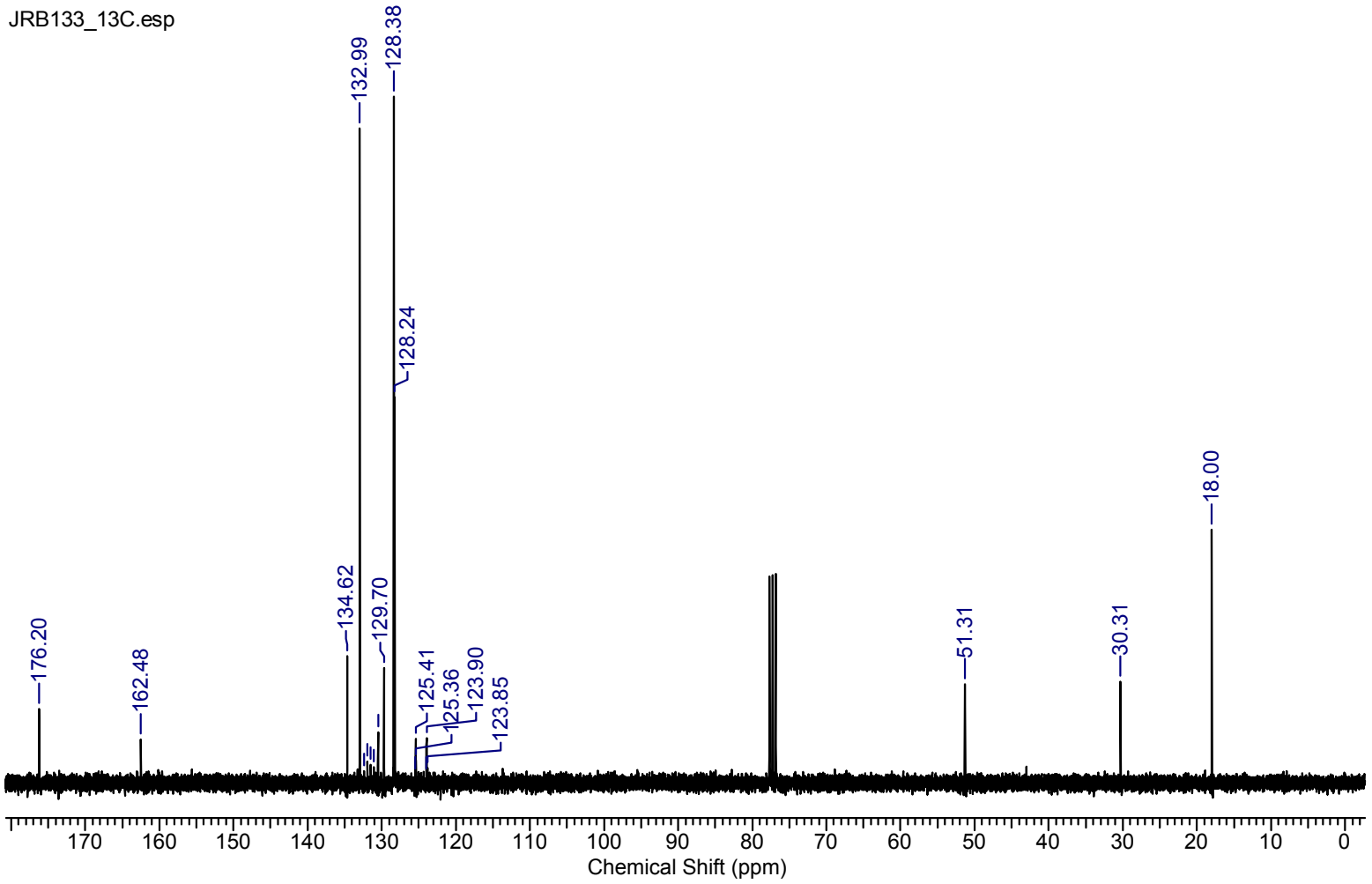
APPENDIX 29B: ^{13}C NMR CLOSE-UP FOR COMPOUND 67F



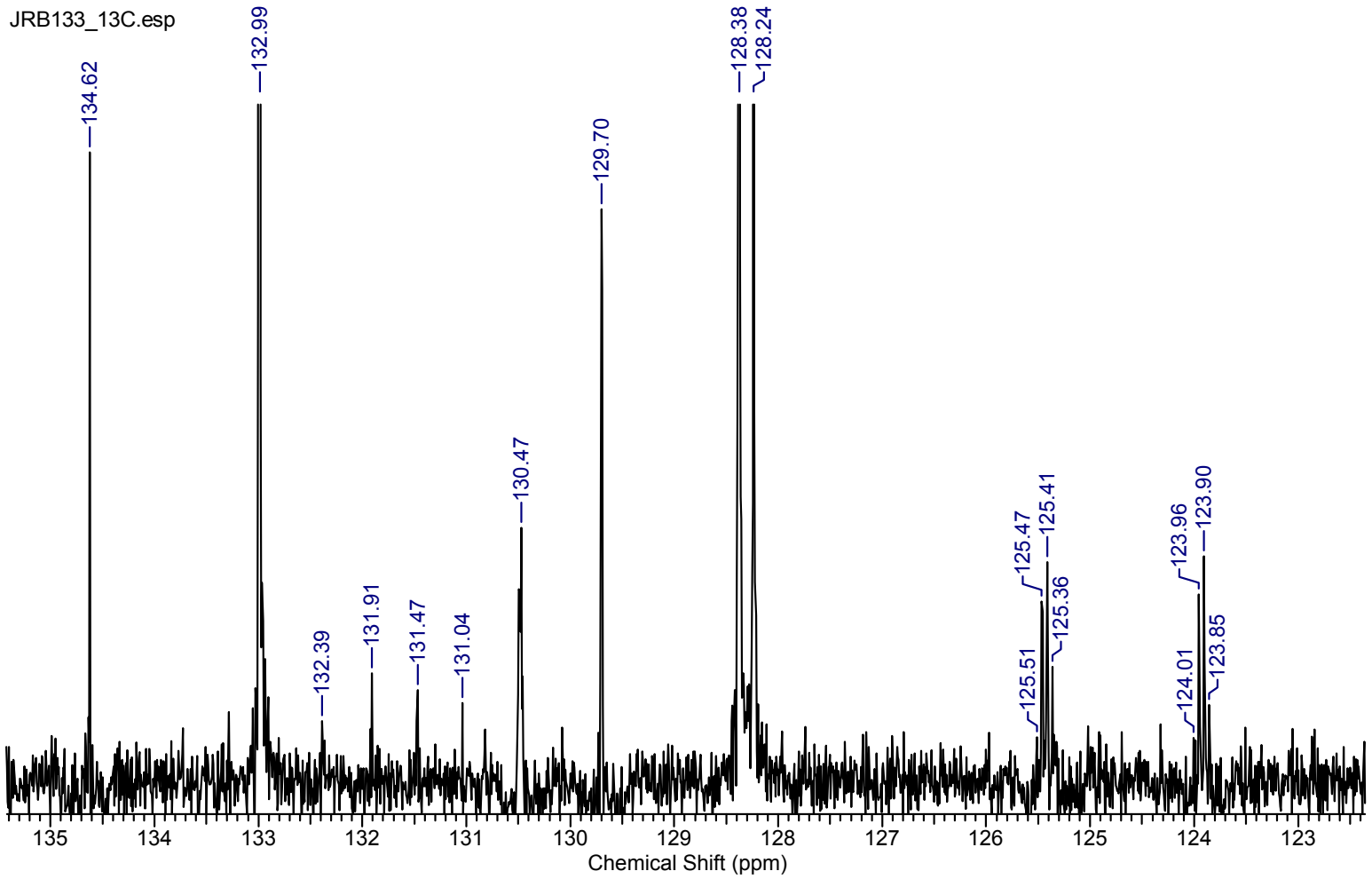
APPENDIX 30: ^{1}H NMR FOR COMPOUND 67G



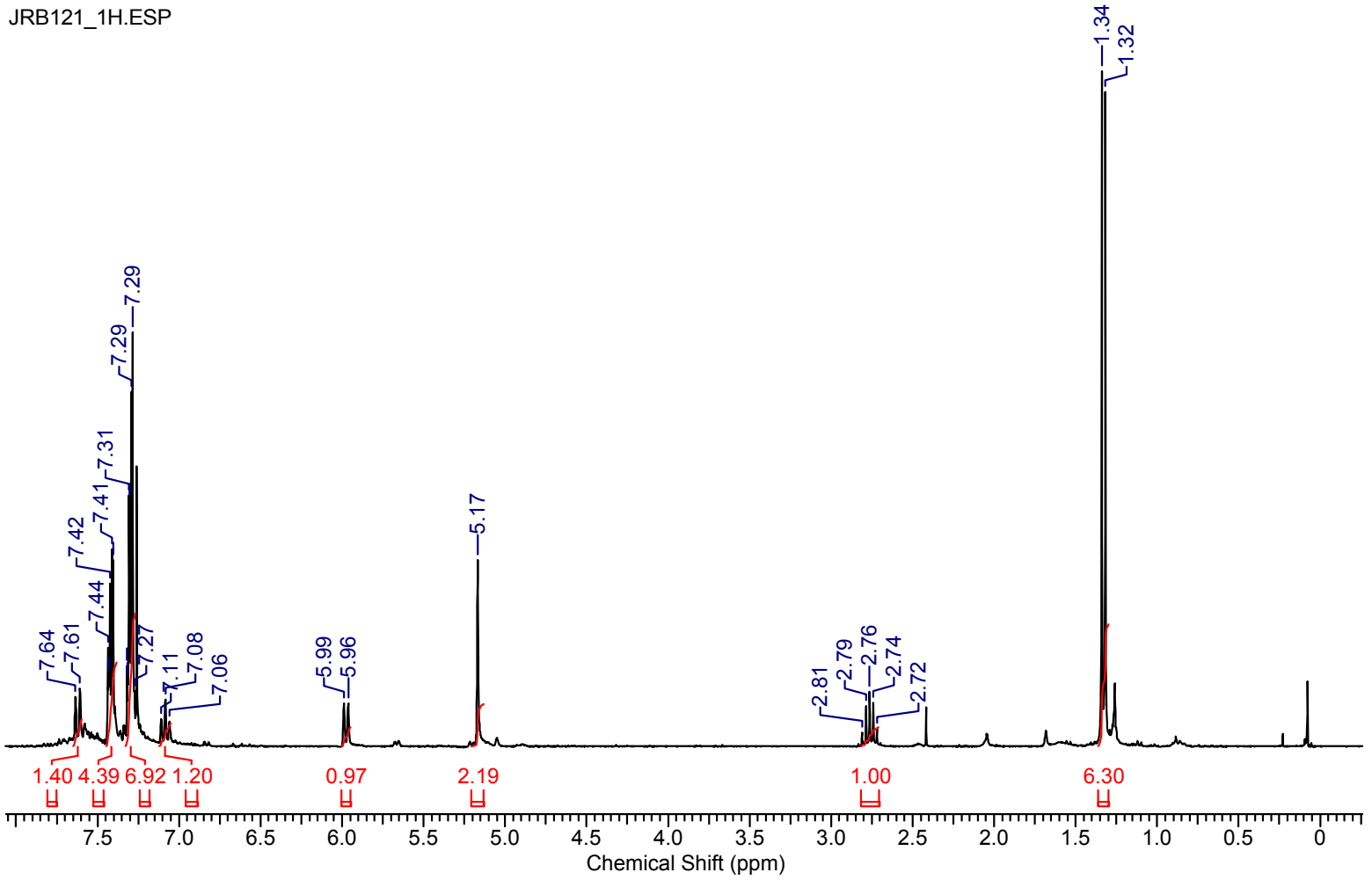
APPENDIX 31A: ^{13}C NMR FOR COMPOUND 67G



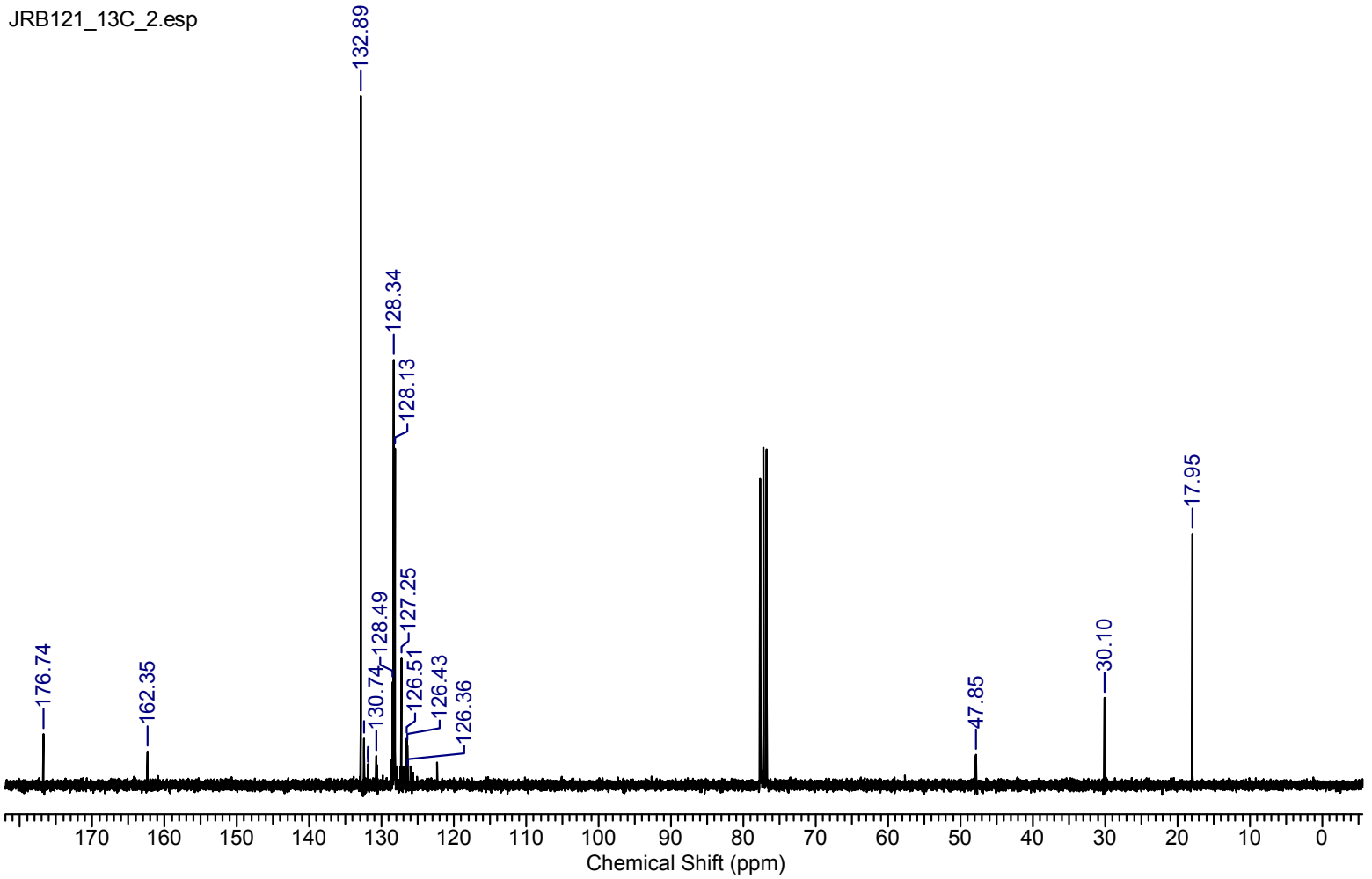
APPENDIX 31B: ^{13}C NMR CLOSE-UP FOR COMPOUND 67G



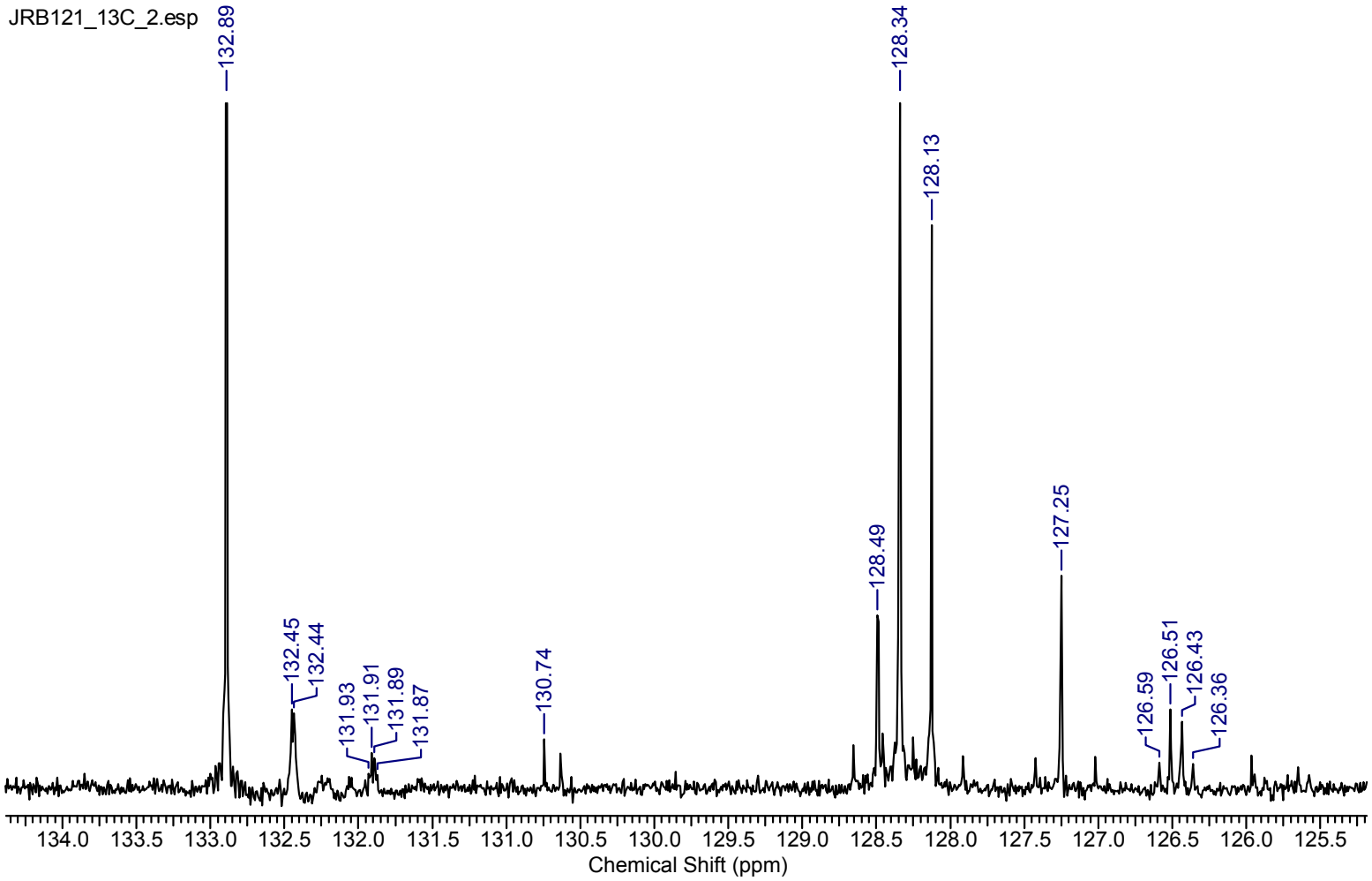
APPENDIC 32: ^{1}H NMR FOR COMPOUND 67H



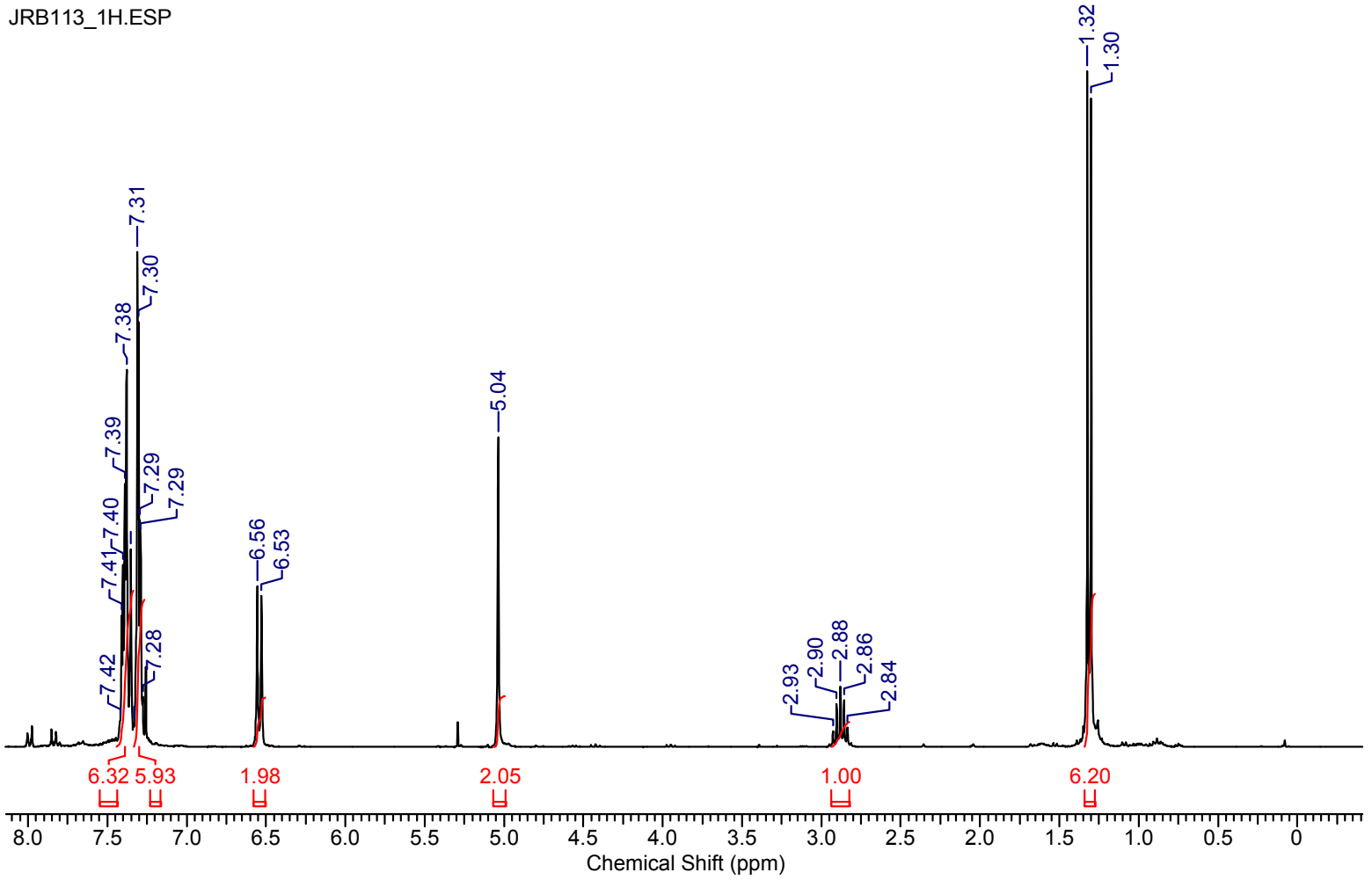
APPENDIX 33A: ^{13}C NMR FOR COMPOUND 67H



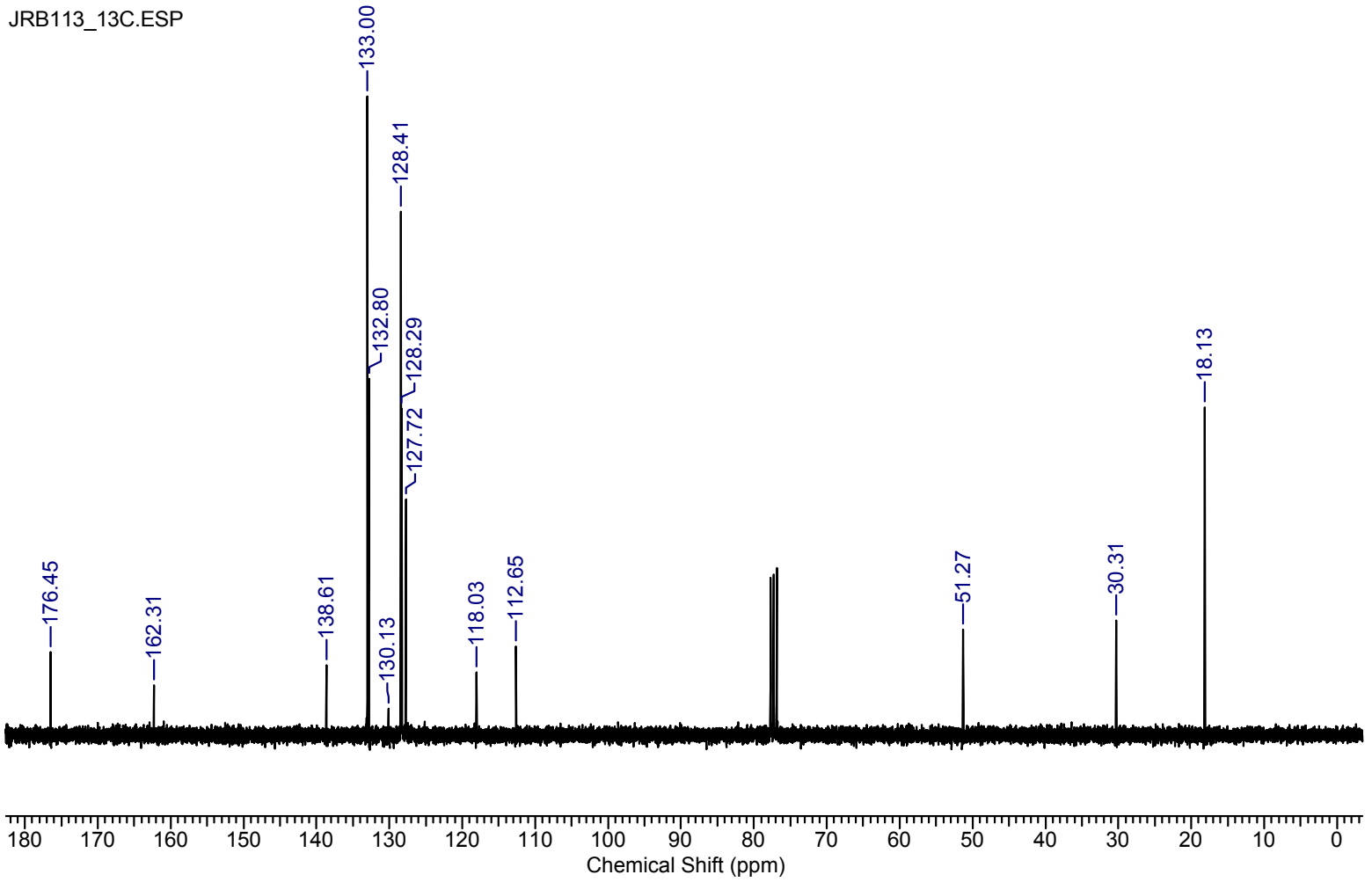
APPENDIX 33B: ^{13}C NMR CLOSE-UP FOR COMPOUND 67H



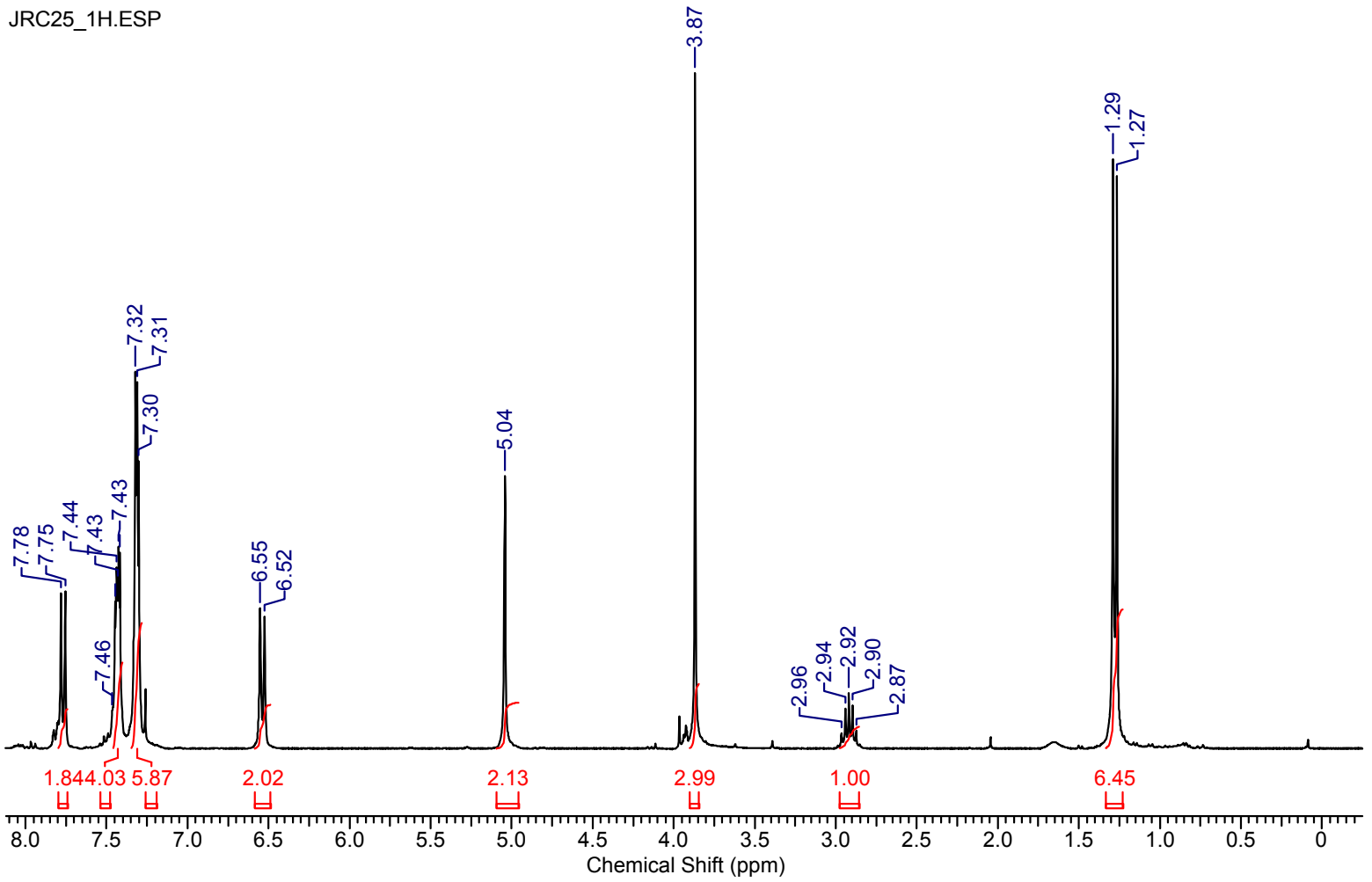
APPENDIX 34: ^{1}H NMR FOR COMPOUND 67I



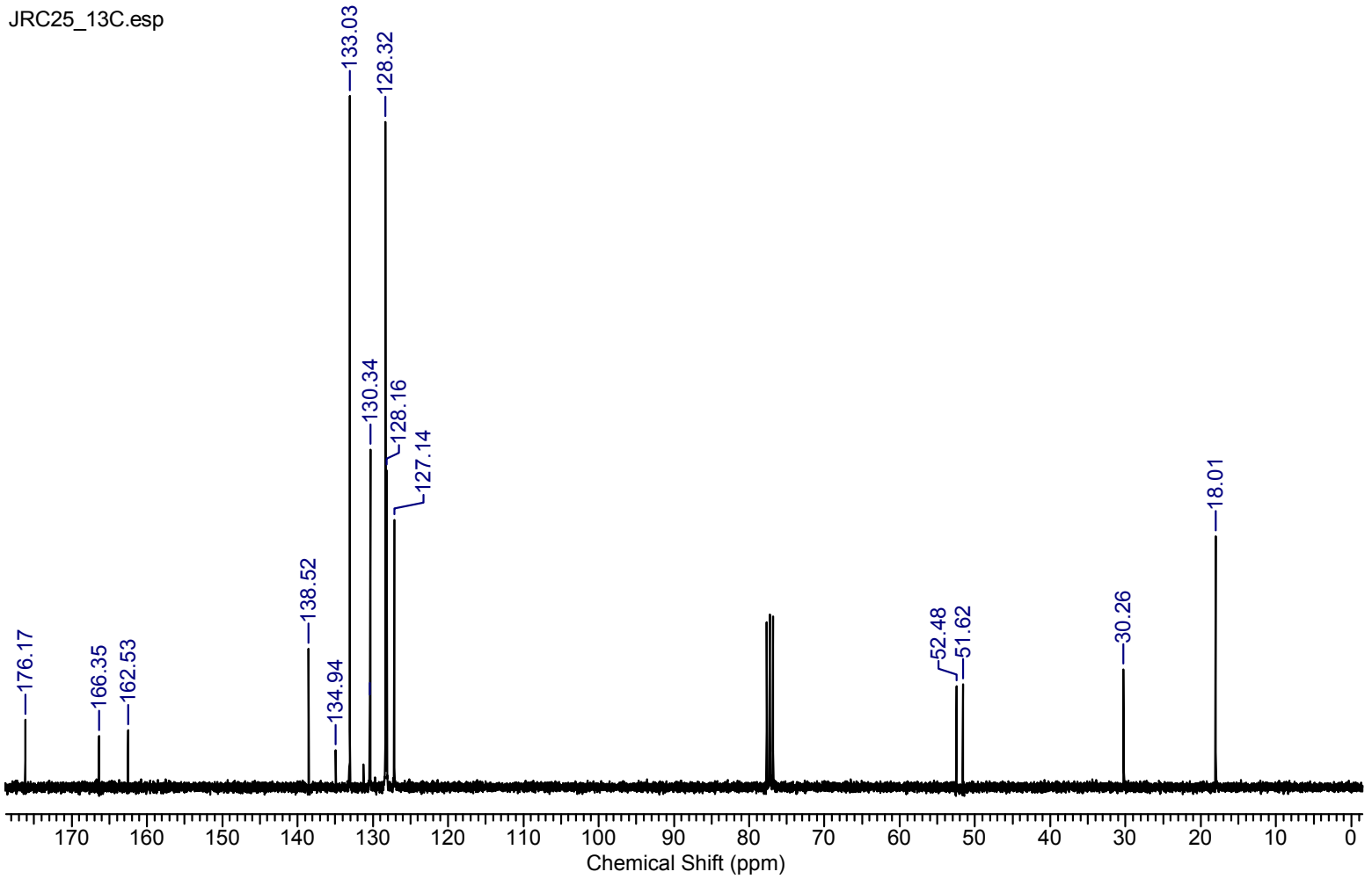
APPENDIX 35: ^{13}C NMR FOR COMPOUND 67I



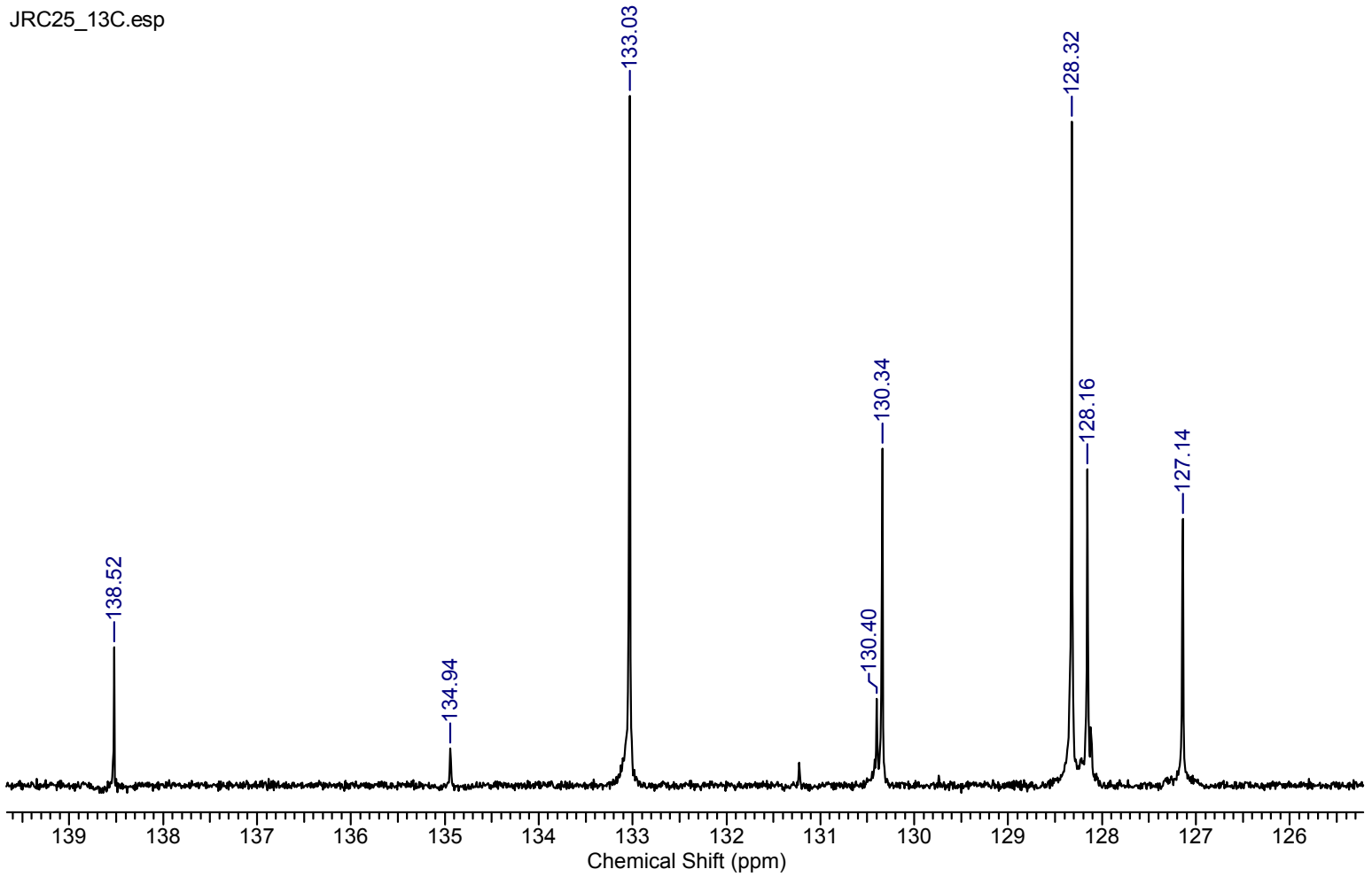
APPENDIX 36: ^{1}H NMR FOR COMPOUND 67L



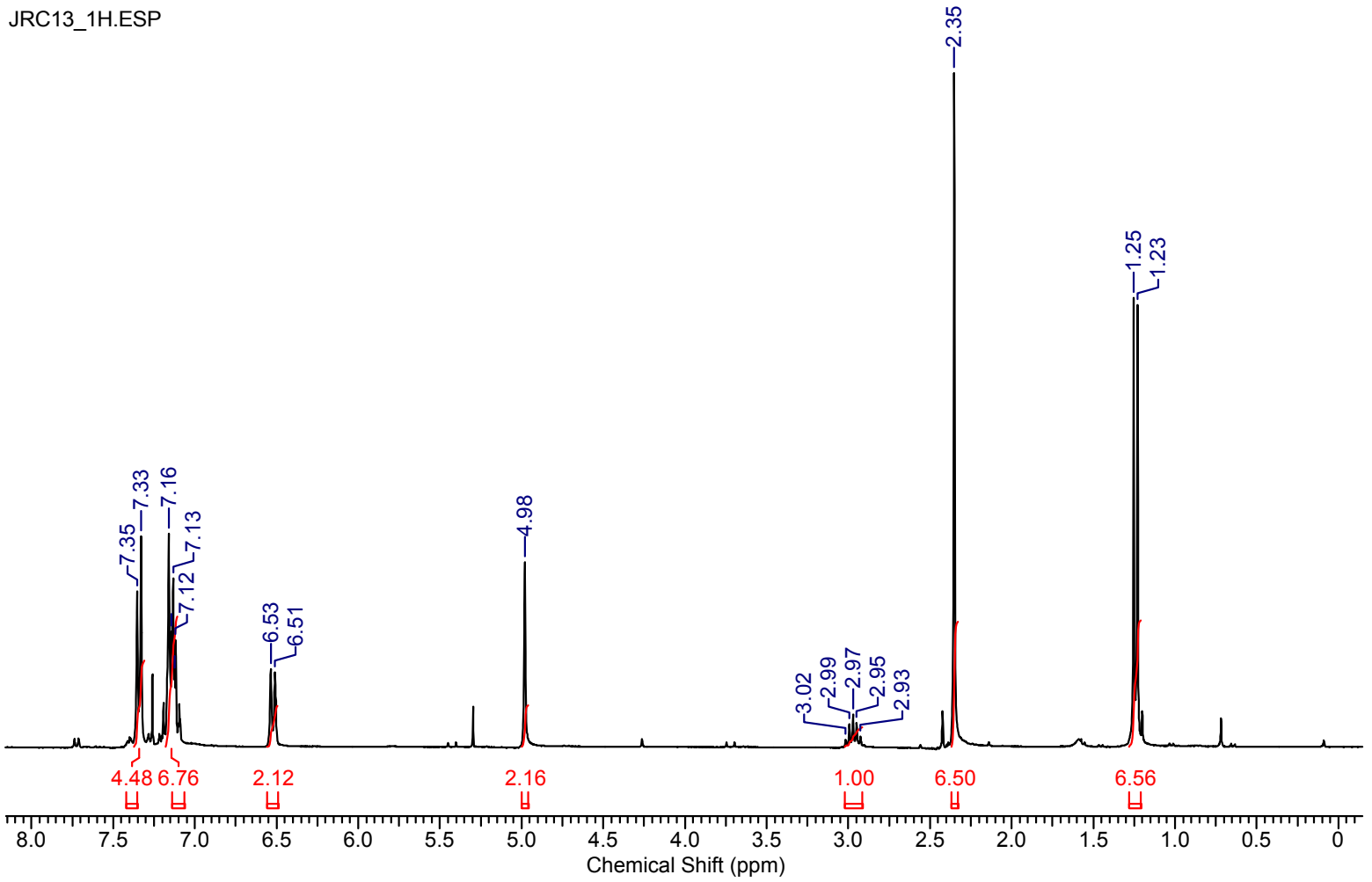
APPENDIX 37A: ^{13}C NMR FOR COMPOUND 67L



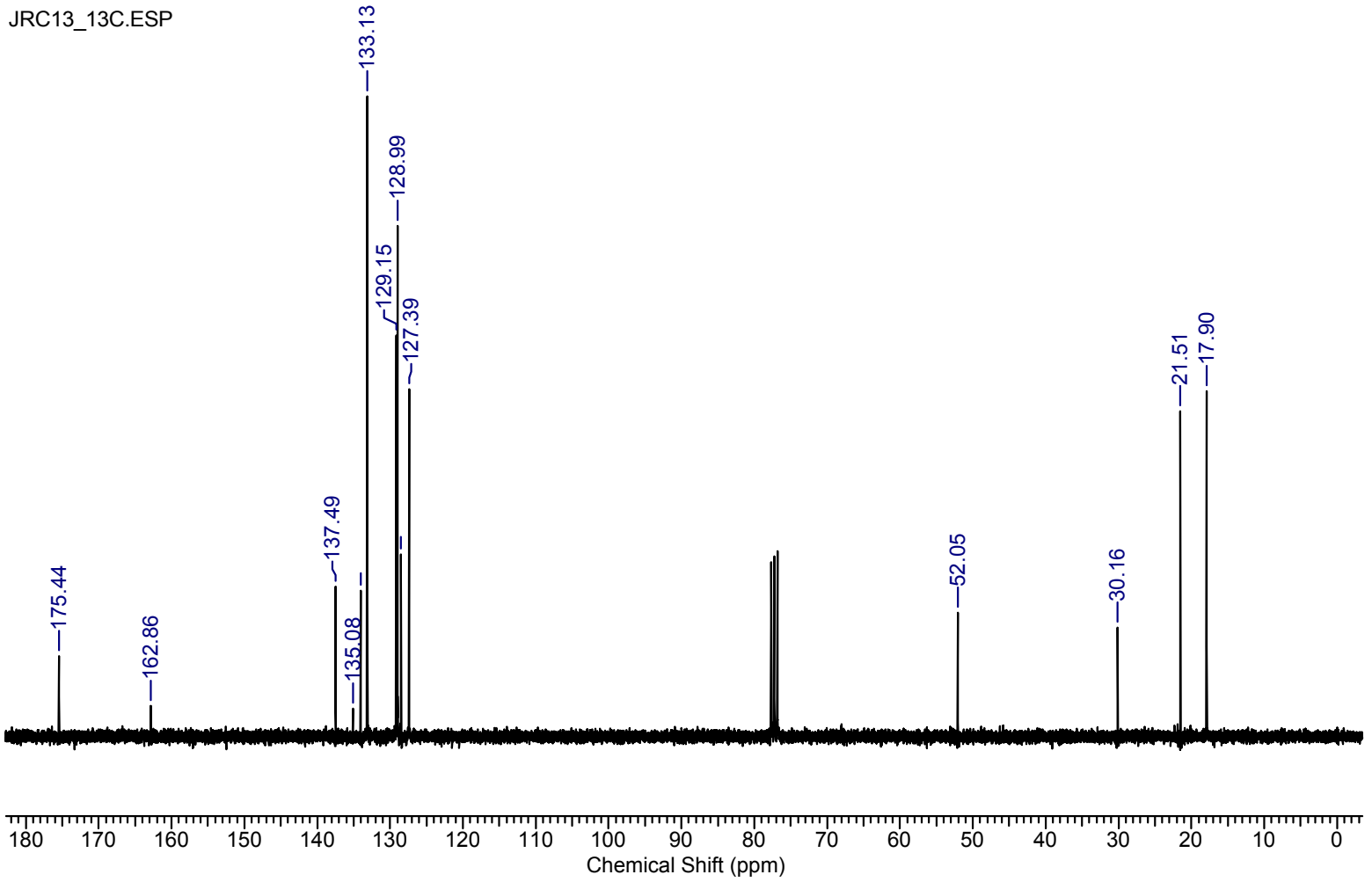
APPENDIX 37B: ^{13}C NMR CLOSE-UP FOR COMPOUND 67L



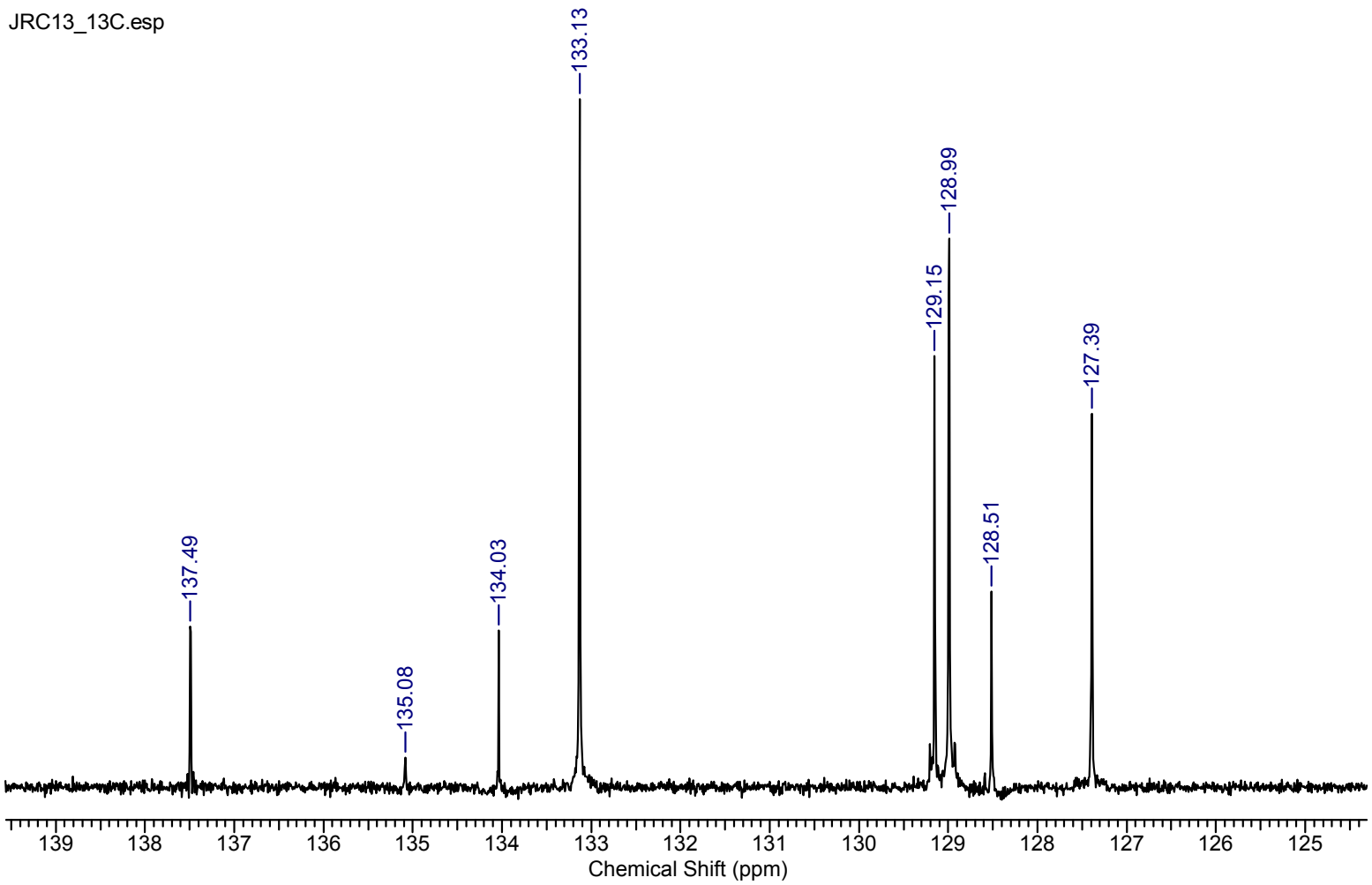
APPENDIX 38: ^{1}H NMR FOR COMPOUND 68A



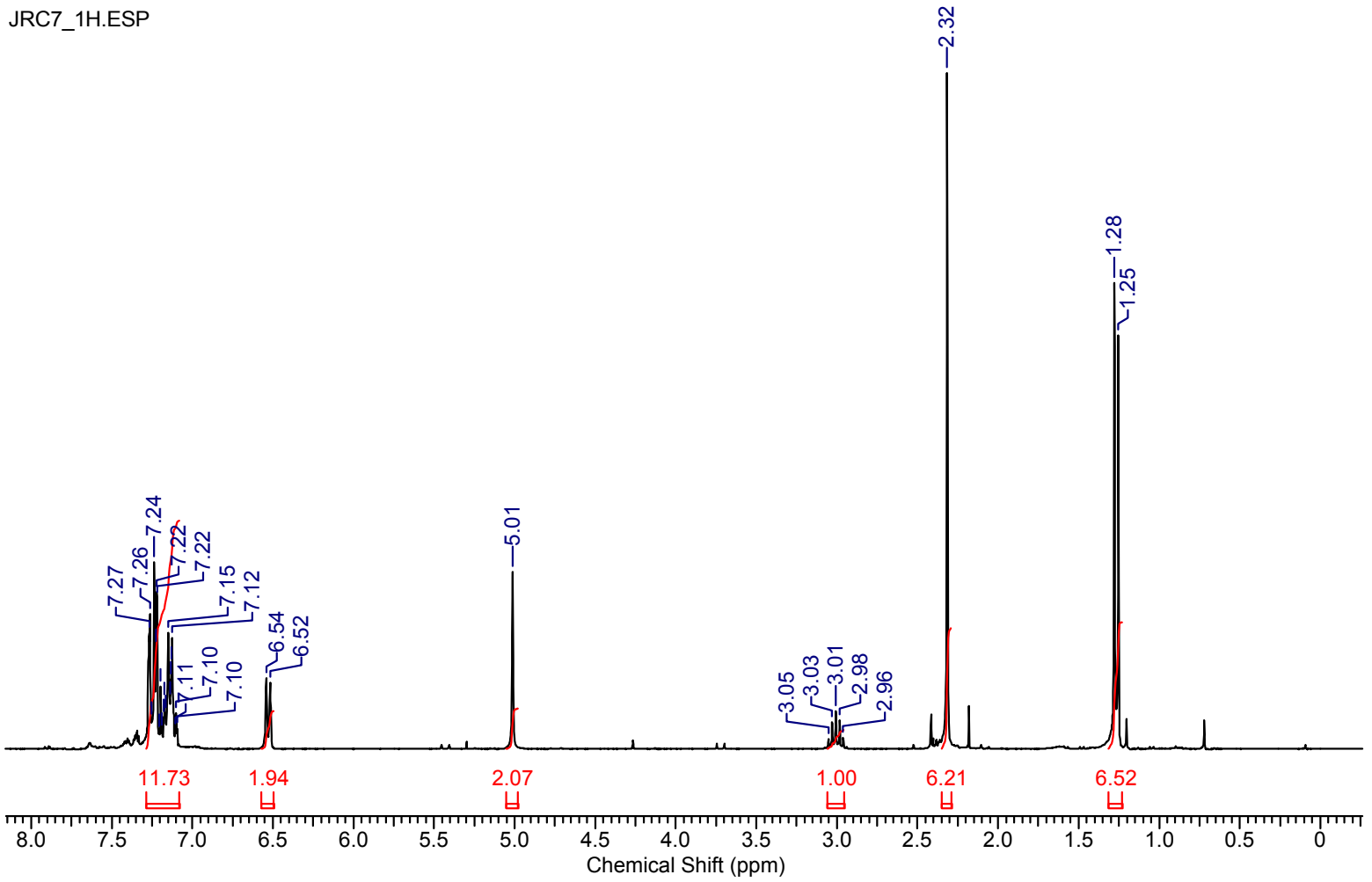
APPENDIX 39A: ^{13}C NMR FOR COMPOUND 68A



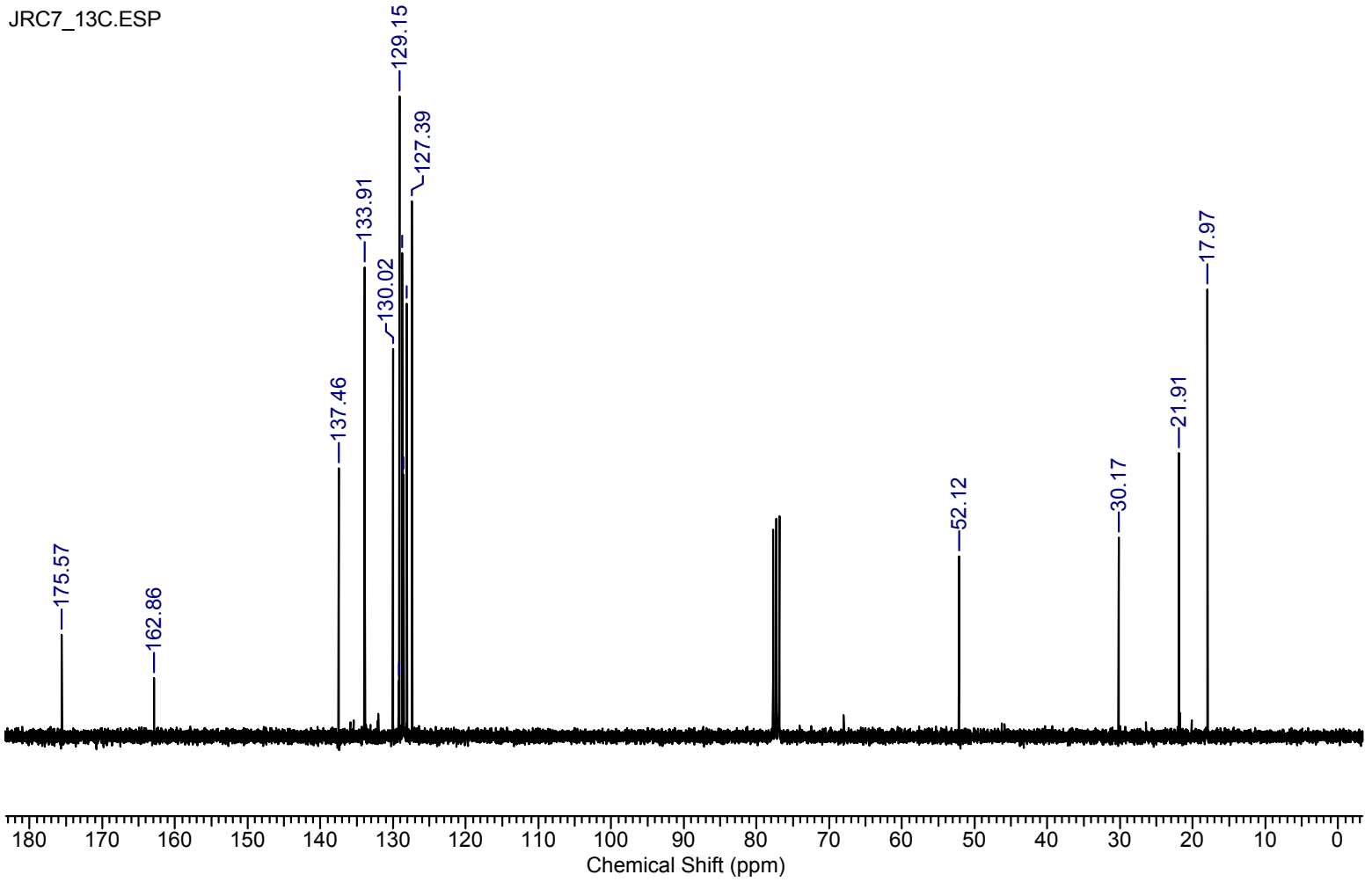
APPENDIX 39B: ^{13}C NMR CLOSE-UP FOR COMPOUND 68A



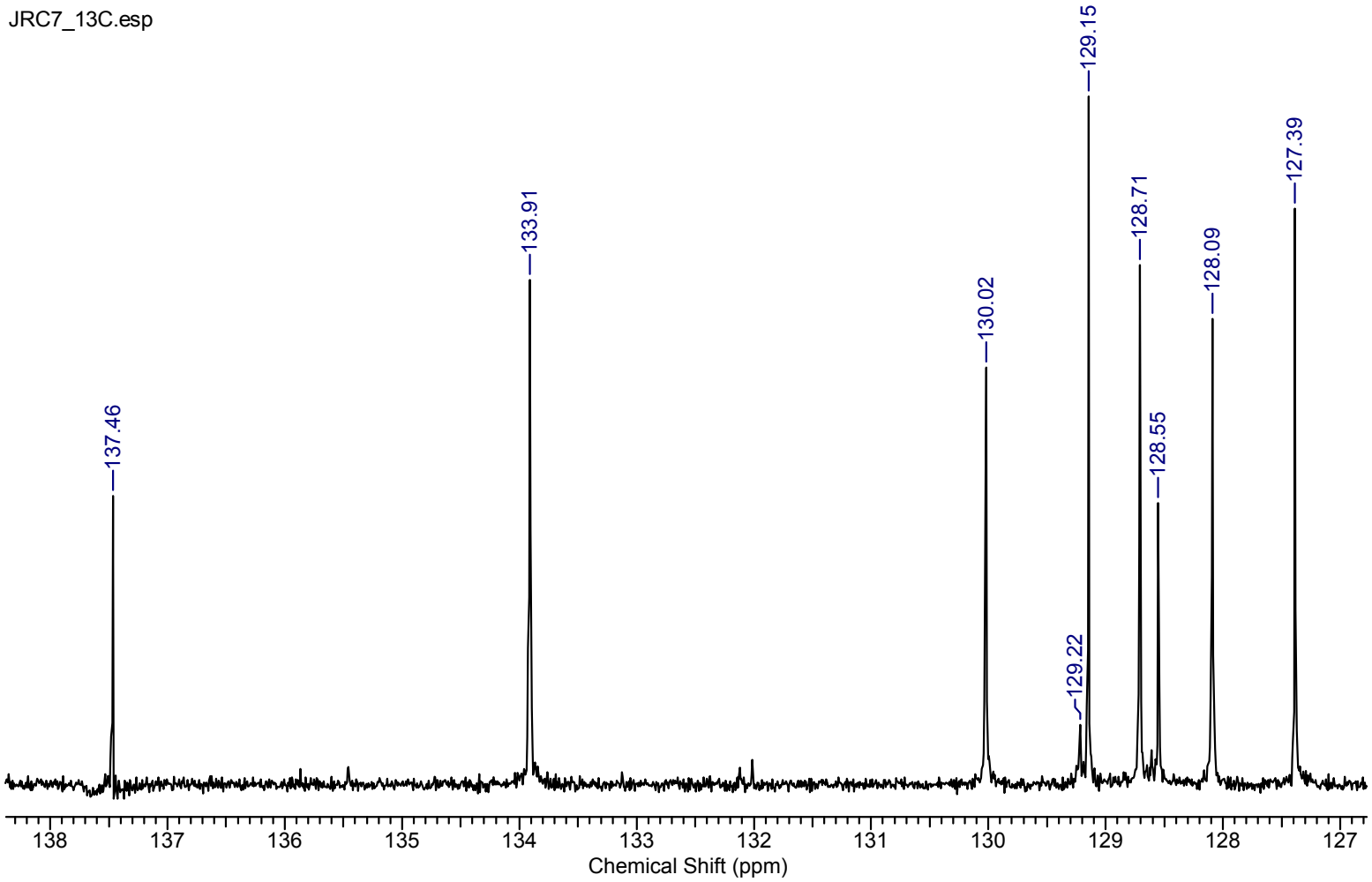
APPENDIX 40: ^{1}H NMR FOR COMPOUND 68B



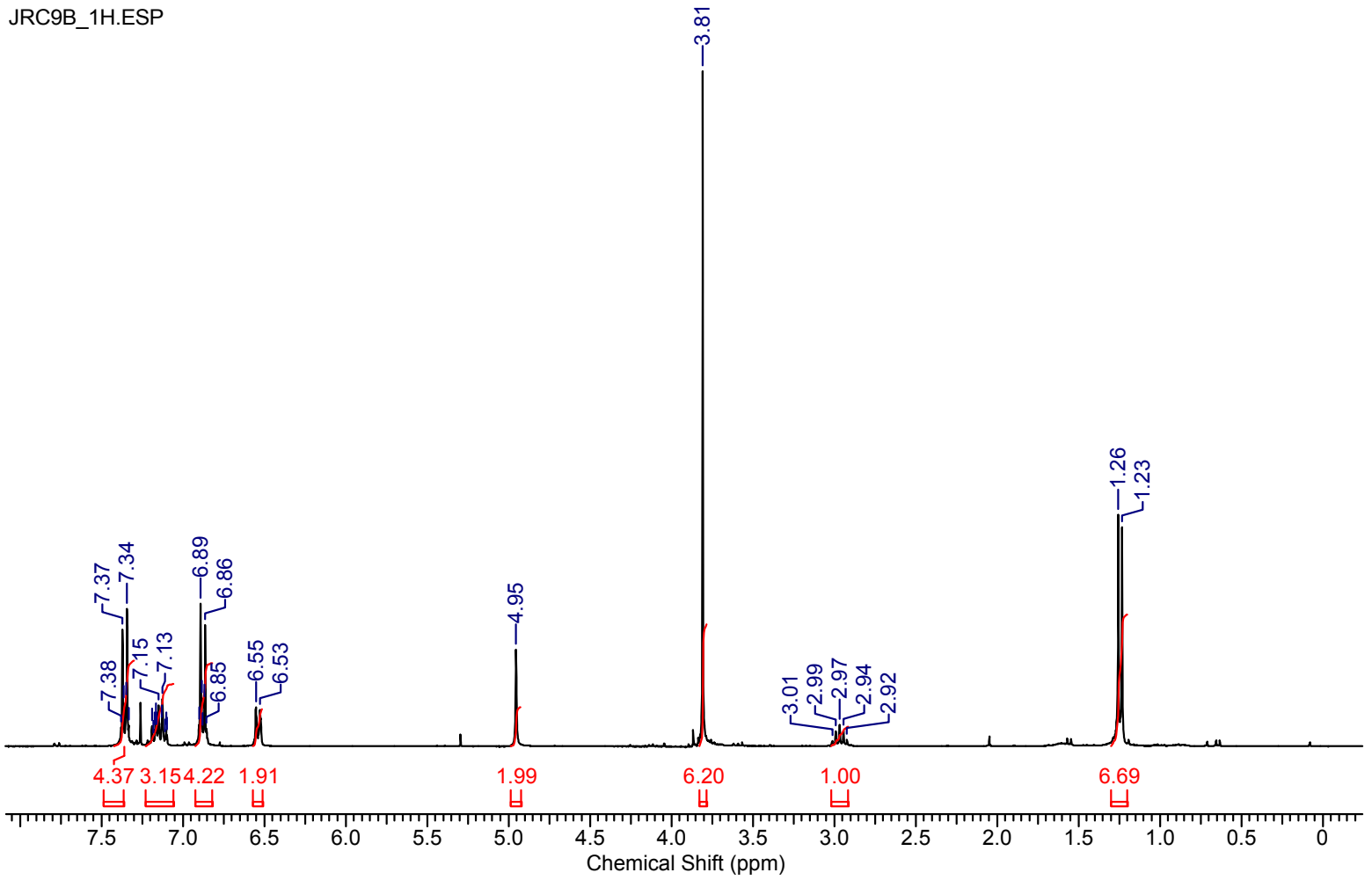
APPENDIX 41A: ^{13}C NMR FOR COMPOUND 68B



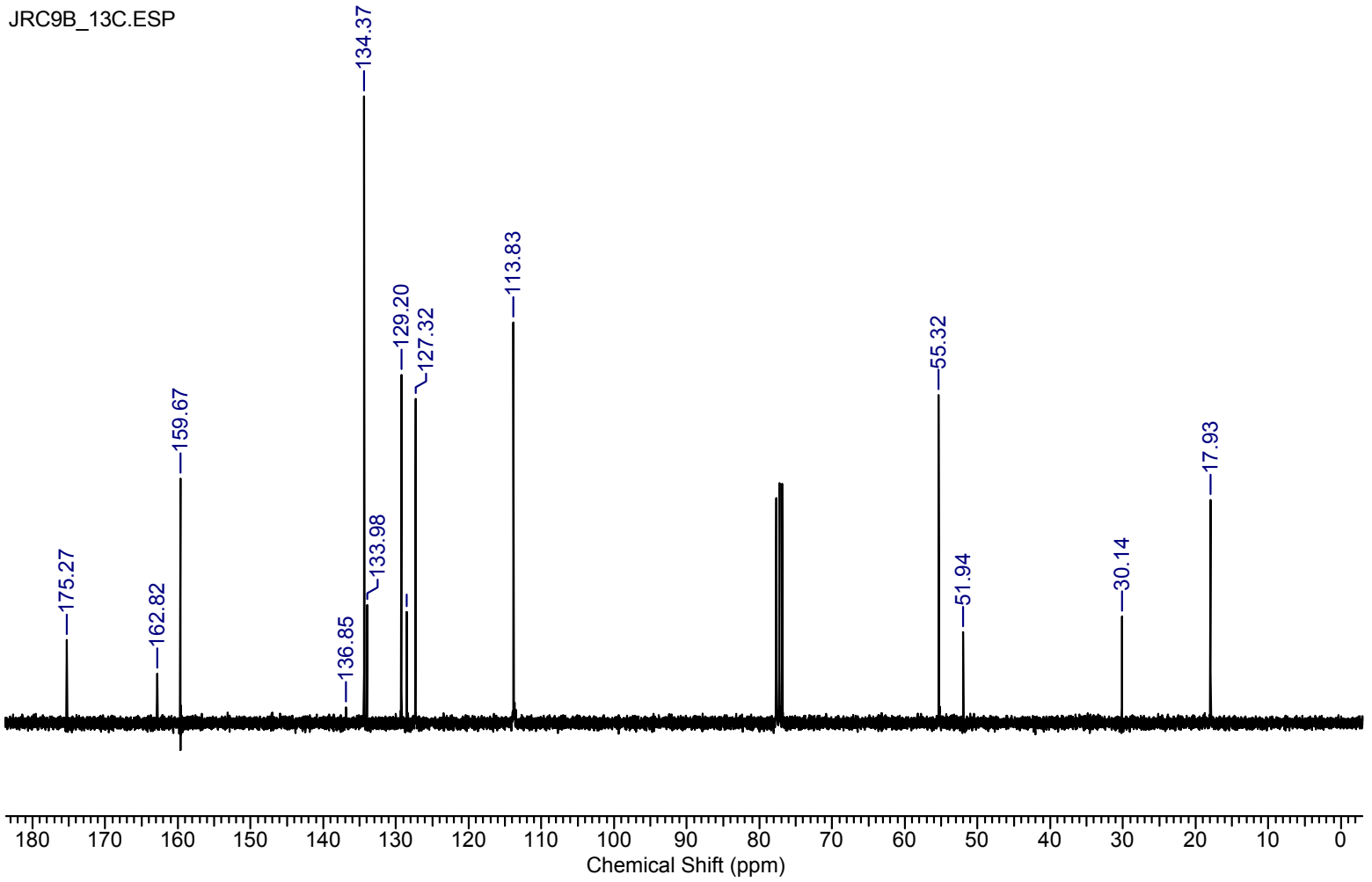
APPENDIX 41B: ^{13}C NMR CLOSE-UP FOR COMPOUND 68B



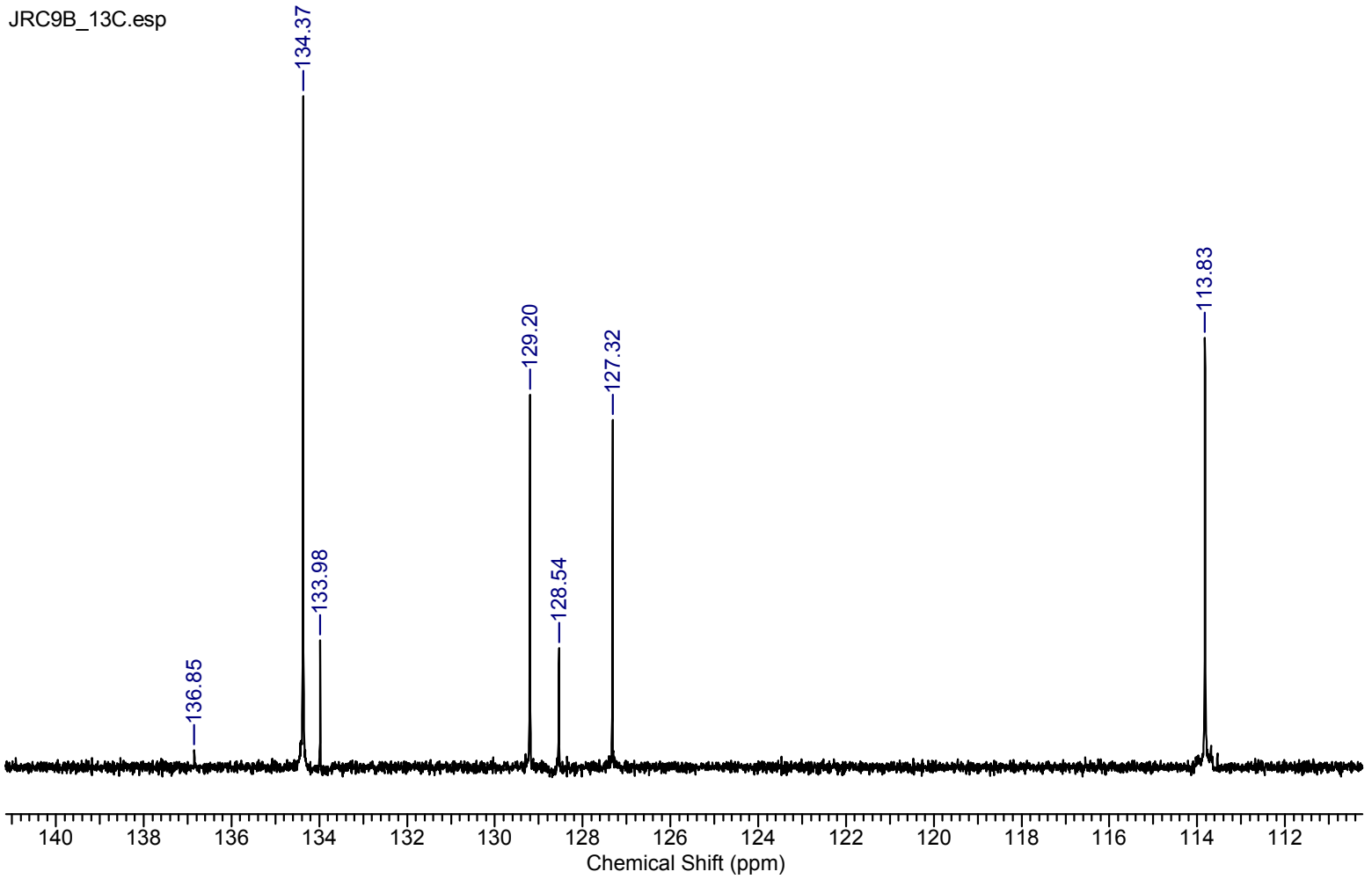
APPENDIX 42: ^{1}H NMR FOR COMPOUND 68C



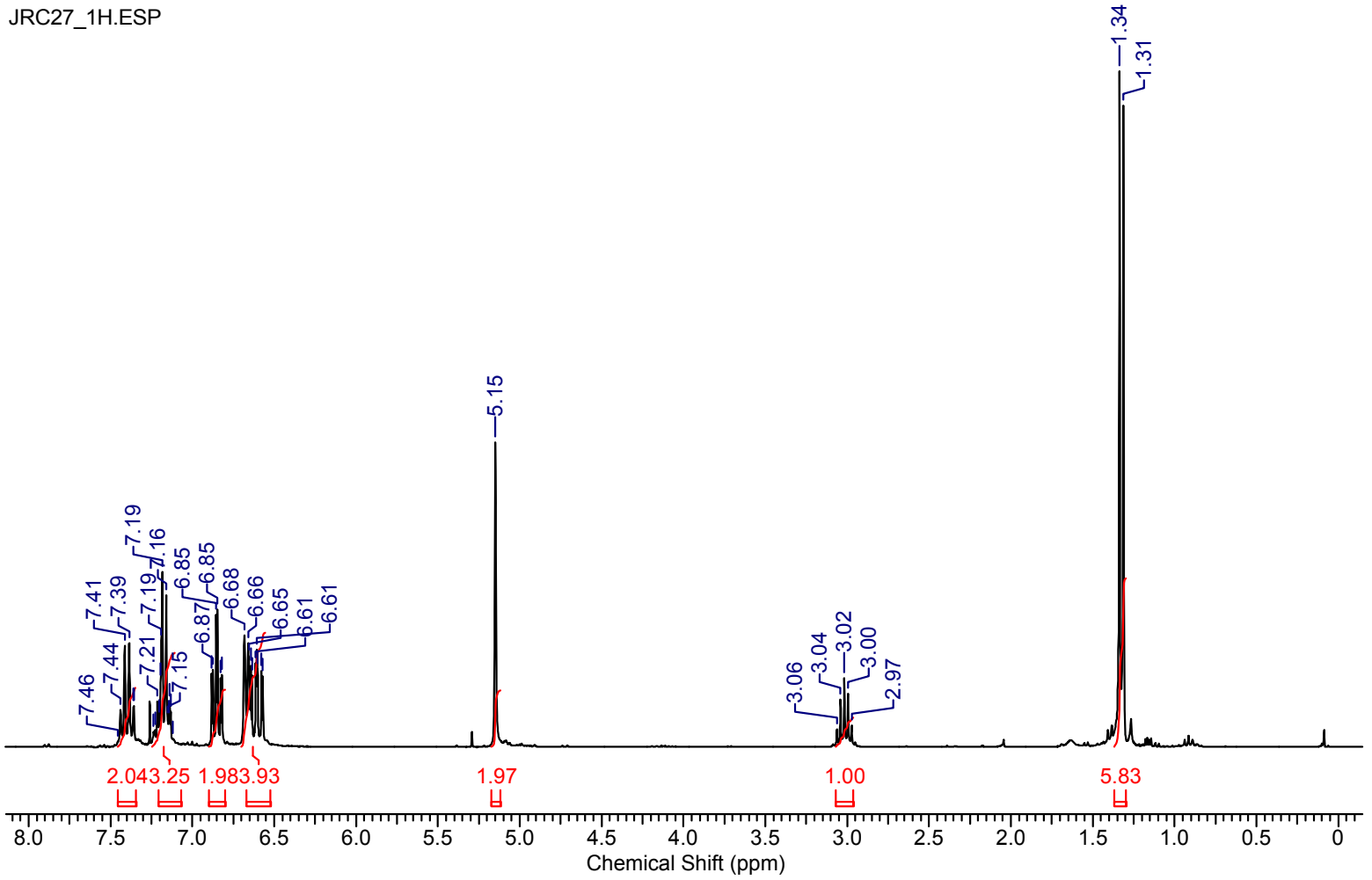
APPENDIX 43A: ^{13}C NMR FOR COMPOUND 68C



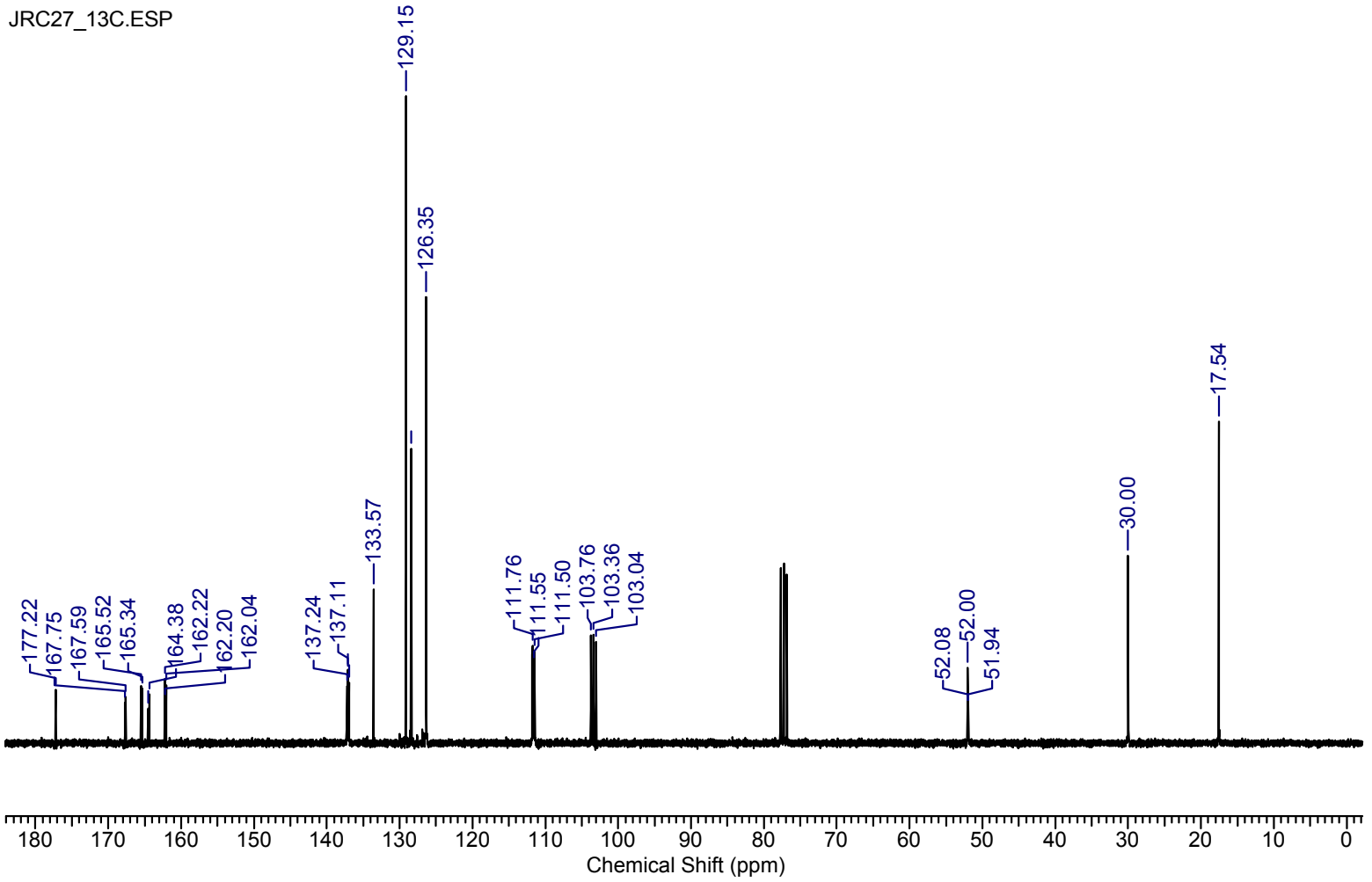
APPENDIX 43B: ^{13}C NMR CLOSE-UP FOR COMPOUND 68C



APPENDIX 44: ^{1}H NMR FOR COMPOUND 68D

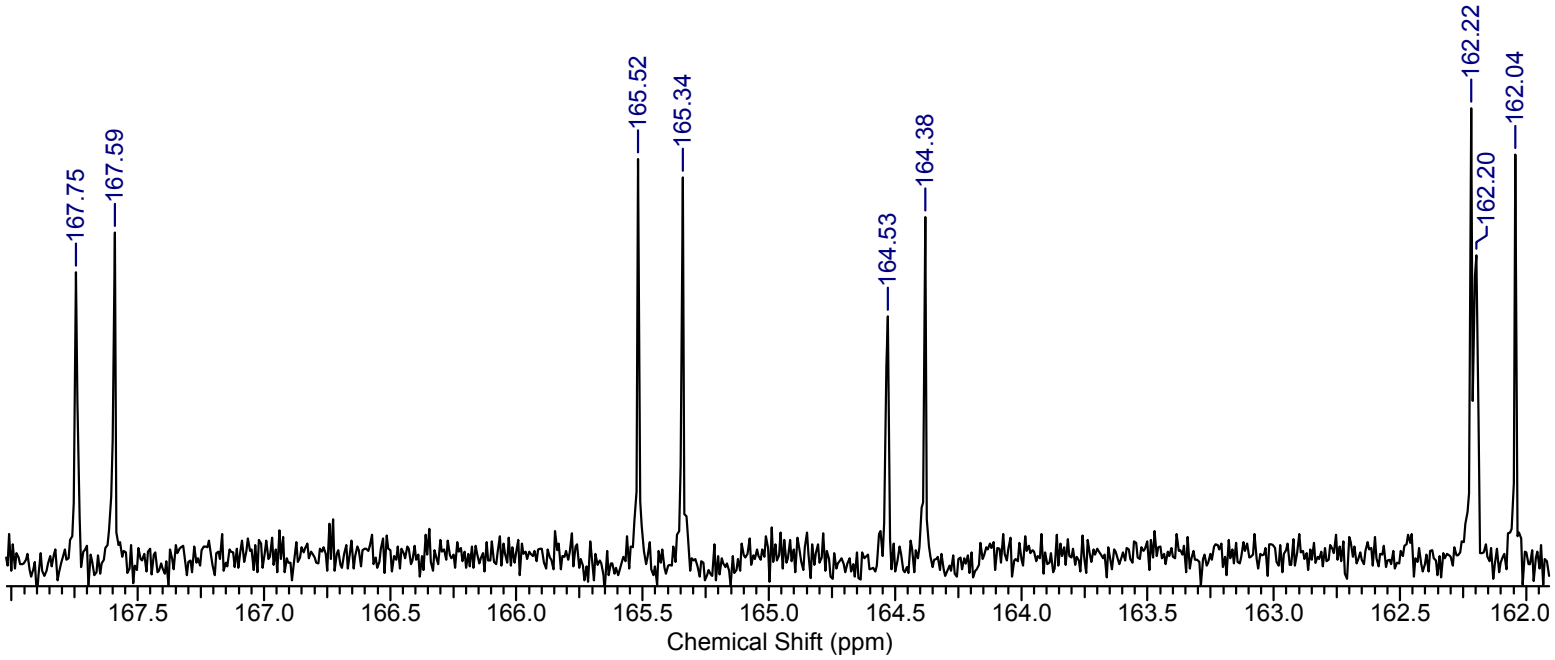


APPENDIX 45A: ^{13}C NMR FOR COMPOUND 68D

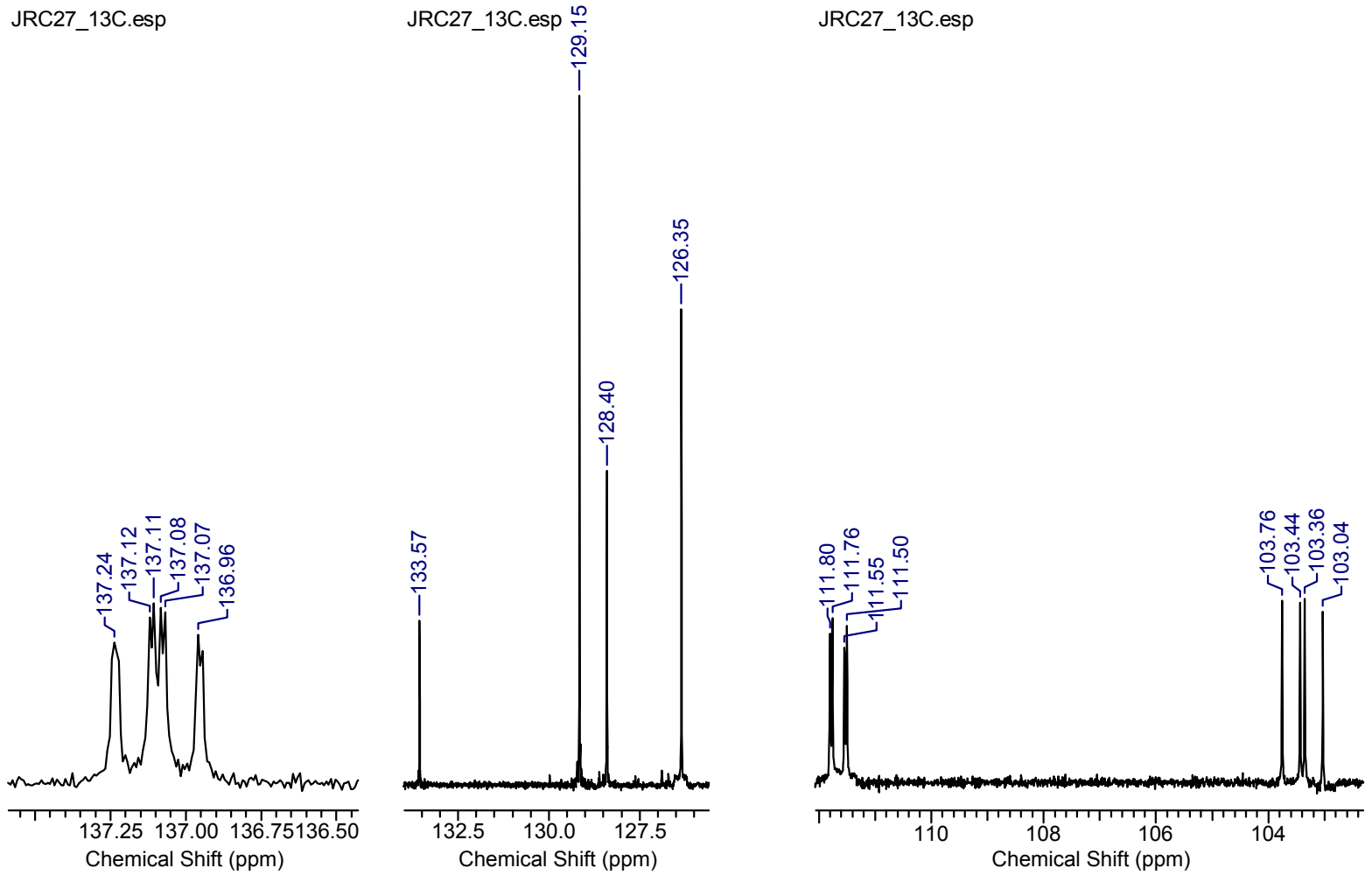


APPENDIX 45B: 1ST ^{13}C NMR CLOSE-UP FOR COMPOUND 68D

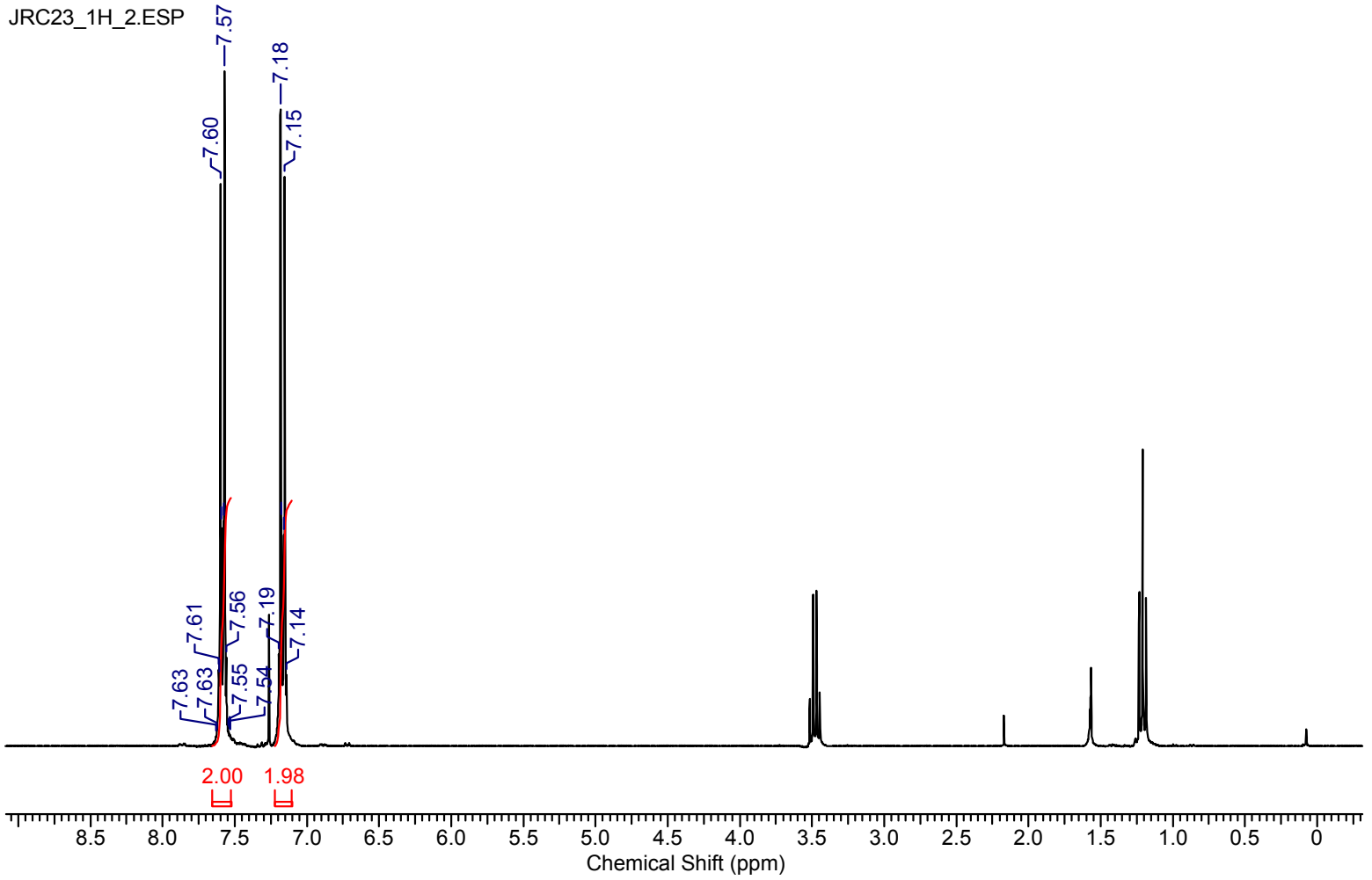
JRC27_13C.esp



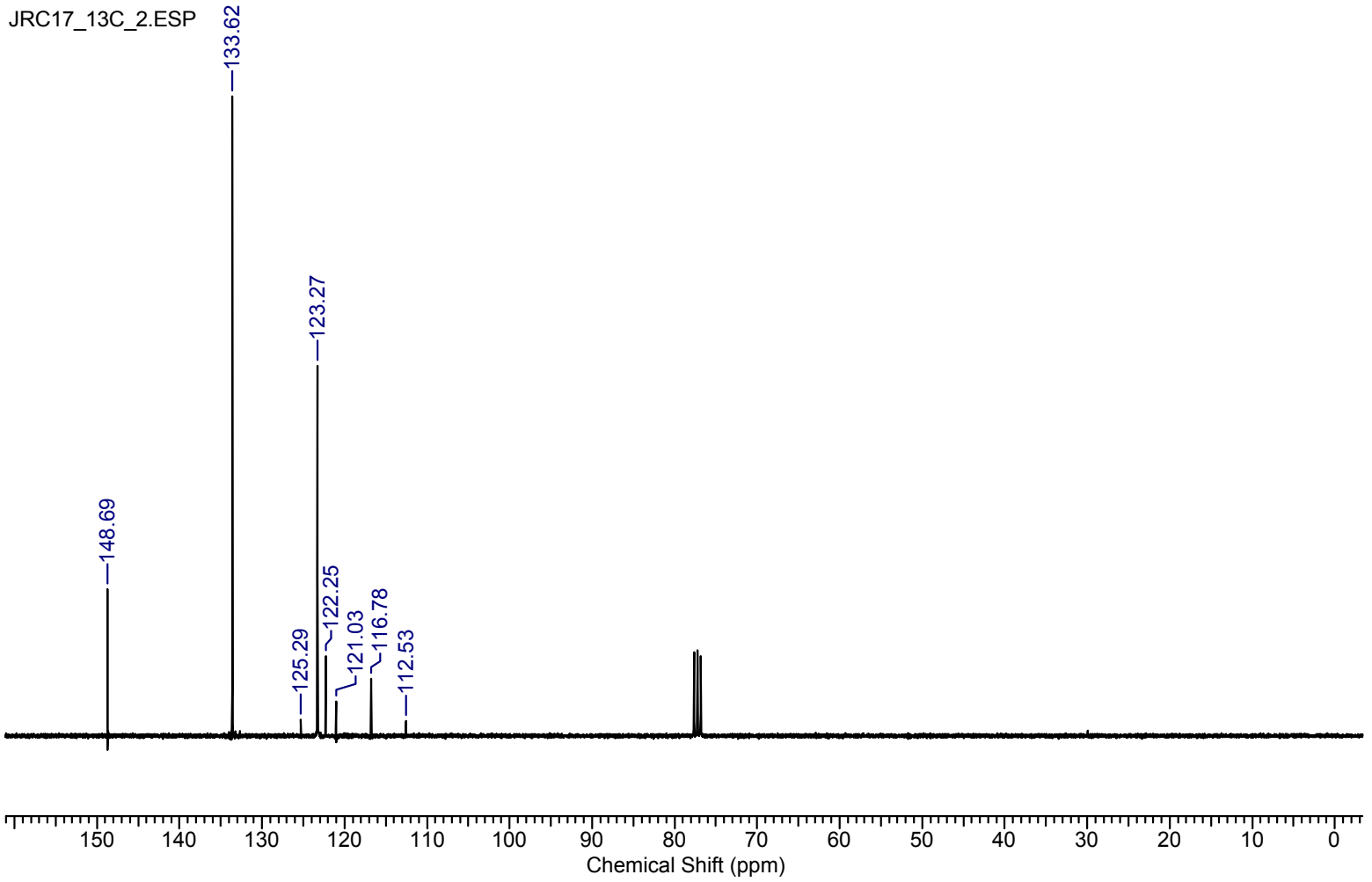
APPENDIX 45C: 2ND ^{13}C NMR CLOSE-UP FOR COMPOUND 68D



APPENDIX 46: ^{1}H NMR FOR COMPOUND 70



APPENDIX 47: ^{13}C NMR FOR COMPOUND 70



APPENDIX 48: ^{1}H NMR FOR COMPOUND 72